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

006897

JUN 17 1988

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

INERT INGREDIENT INFORMATION IS NOT INCLUDED

MEMORANDUM

SUBJECT: TB Project No. 8-0601. EPA ID No. 4822-294.
Fenoxycarb: 21-Day Inhalation Study in the Rat.

Tox. Chem. No. 652C

FROM: David G. Van Ormer, Ph.D.
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Hazard Evaluation Division (TS-769C)

TO: Joseph M. Tavano
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THRU: Marcia van Gemert, Ph.D.
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and

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Hazard Evaluation Division (TS-769C)

Background:

TB Memo of October 21, 1986 stated that the remaining data gap for TB approval of EPA ID No. 4822-EOU is a 21-day inhalation study (as an aerosol) with a mass median aerodynamic diameter of 1 µm. The same memo discussed the toxicological consideration of the other active ingredient, [redacted]. The conclusion was that the exposure scenario for the proposed formulation does not differ significantly from existing uses of these component chemicals. Separately, the memo requested that label precautionary statements for acute inhalation and dermal toxicity (both Category III) conform more closely to the required wording.

A review of the requested inhalation study is attached

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Reviewed by: David G. Van Ormer, Ph.D. D.V.O. 12-11-87 006897
Section III, Tox. Branch (TS-769C)
Secondary Reviewer: Marcia van Gemert, Ph.D.
Section III, Tox. Branch (TS-769C)

DATA EVALUATION REPORT

STUDY TYPE: Subacute Inhalation-Rat TOX. CHEM. NO.: 652C

TEST MATERIAL: RO 13-5223/000 MRID No.: 403558-01

SYNONYS: Fenoxycarb, Technical, 96.6%

STUDY NUMBER: 085500

SPONSOR: F. Hoffmann-LaRoche and Co., AG

TESTING FACILITY: RCC, Research and Consulting Co., AG

TITLE OF REPORT: Subacute (28-day) Repeated Dose Inhalation Toxicity Study with RO 13-5223/000 in the Rat.

AUTHOR(S): D.M. Bernstein, H. Luetkemeier, et al.

REPORT ISSUED: June 17, 1987

Summary and Conclusions:

Dose groups of five rats of each sex received inhalation exposure to technical fenoxycarb at doses of 0.0, 0.01, 0.10, and 1.13 mg/l. Administration was for 6 hours/day, 5 days/week for a total of 21 days. The top dose group contained 5 additional rats per sex, subjected to a 4-week post-treatment recovery. The exposure system was that of Sachsse et al., a flow-past nose-only design. Results of particle sizing showed that 97% had a diameter of 3 µm or less. There were no signs of toxicity, but at top dose the males showed decreased body weight gain and the females exhibited increased absolute liver weights.

Label precautionary statements, as previously noted, do not conform to required wording.

NOEL = 0.10 mg/l
LOEL = 1.13 mg/l (HDT)
(decreased body weight gain in males and increased absolute liver weight in females)

Classification: Guideline

A. MATERIALS

1. Test material: identified by code No. RO 13-5223/000, Batch No. 2. Described as a solid of 96.6% purity. The test material was stated as "stable for several years" in the solvent, ethyl alcohol, under room conditions. Contaminants were not reported.

2. Test animals: SPF-bred Wistar rats, obtained from KFM, Kleintierfarm Madoerin AG. At pretest the males were 9 weeks of age and weighed 190-228g, and females were 11 weeks and weighed 130-208g. Identification was by cage number and neck tag. There was a 7-day acclimation after veterinary examination. The animals were housed individually in Makrolon type-3 cages with wire mesh tops and granulated softwood bedding. Air conditioning in the animal room included 10-15 air changes/hour, with a temperature of 19-25°C, relative humidity at 40-70%, and a light/dark cycle of 12 hours fluorescent light per day. The diet was pelleted Kliba No. 343, rat maintenance diet. A certificate of analysis for specified batches is attached to the Report. The tap water was analyzed for chemical and bacteriological contaminants. Both the feed and water were available ad libitum.

B. STUDY DESIGN

1. Animal Assignment

The animals were randomly assigned by a computer-generated algorithm to four inhalation dose groups (including control), each containing five rats of each sex. Below are tabulated the nominal, gravimetric, and analytic concentrations administered by continuous daily inhalation exposure for 6 hours/day, 5 days/week for a total of 21 exposures.

Group	Dose Level (mg / l air)	Inhalation Concentration	
		GRAVIMETRIC (mg / l air) Mean (Std. Dev)	ANALYTICAL (mg / l air) Mean
1 (alcohol control)	0	0.0015(0.001)	0
2	0.01	0.011 (0.002)	0.010
3	0.1	0.099 (0.009)	0.103
4	1.0	1.05 (0.10)	1.131

The particle size determination measurements showed that 97.4 % (std. Dev. 1.91) of the particles by weight were found on the 3 µm stage of the impactor or less.

The reversibility of treatment-related changes was studied with 5 additional animals per sex in group 4 (only) over a 4-week recovery period.

2. Exposure System

At the end of this section are reproduced pages 16 to 19 of the Report, describing the inhalation exposure system, aerosol generation, and test material and particle size determination. The system is that of Sachsse et al., which is a flow-past, nose-only design, in which the animals are placed separately in tubes, positioned radially around the exposure chamber. The internal active volume of the chamber for exposing 40 animals by nose-only is one liter. Equilibration time is 34 seconds. The unique feature is stated to be the conduction of "fresh" aerosol to each individual animal. The system eliminates "rebreathing" and, also, depletior of aerosol, which are common problems in standard exposure systems. Air flow was 1.25 l/min/animal.

Aerosol of test material "was generated by a constant volume reservior feeding a Hospitak No. 950 nebulizer following dissolution with ethyl alcohol." Nebulizer output was then diluted with clean air to the concentrations required for the study. The aerosol generation system was adjusted to achieve the intended aerosol concentrations, each with a mass median aerodynamic diameter of 3 µm or less. The control group was exposed to nebulized ethyl alcohol using a similar system.

Fenoxycarb toxicology review

Page _____ is not included in this copy.

Pages 5 through 8 are not included in this copy.

The material not included contains the following type of information:

___ Identity of product inert ingredients

___ Identity of product impurities

___ Description of the product manufacturing process

___ Description of product quality control procedures

___ Identity of the source of product ingredients

___ Sales or other commercial/financial information

___ A draft product label

___ The product confidential statement of formula

___ Information about a pending registration action

X FIFRA registration data

___ The document is a duplicate of page(s) _____

___ The document is not responsive to the request

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

Determinations of concentration, particle-size distribution, oxygen content, relative humidity and temperature were performed at the position of the animal's snout in the exposure system. Gravimetric concentration was determined using Gelman Type AE 47-mm diameter glass fiber filters, which were then extracted with acetonitrile for analysis by HPLC. Particle size was determined using a Mercer 7-stage cascade impactor (In-Tox Products, Model 02-1300) with sampling airflow at 1.0 l/min. Oxygen was measured once daily/group using an OXYCOM 25-D (Draegerwerk AG).

3. Statistics

Continuous data were analyzed by a one-way ANOVA followed by either the Dunnett test (Gausian data) or the Steel test, a non-parametric analysis. For mortality data the Fisher exact test for 2 X 2 tables was applied.

4. Quality Assurance

Dates of seven quality assurances inspections are listed.

5. Observations and Exposure Monitoring

a. Analytic concentration: once per exposure period.

b. Gravimetric concentration: twice at high dose, once at other doses.

c. Particle size: twice weekly at high dose and once weekly at other doses.

d. Signs and mortality: once daily.

e. Food consumption (per cage) and body weight: once during acclimation and weekly thereafter.

f. Ophthalmoscopy: once at week 4 after application of a mydriatic (included cornea, lens, anterior chamber, vitreous body, and ocular fundus).

g. Hematology and Clinical Chemistry

Samples were drawn from the retro-orbital plexus at approx. 7:00 AM under light ether anesthesia and after 18-hour fasting. Blood sampling occurred at termination and (for high dose only) one month later, at the end of recovery. For hematology blood samples the anticoagulant was EDTA-K2. The parameters measured are checked (X) as follows:

|X| Hematocrit (HCT)*	| | Total plasma protein (TP)
|X| Hemoglobin (HGB)*	|X| Leukocyte differential count
|X| Leukocyte count (WBC)*	|X| Mean corpuscular HGB (MCH)
|X| Erythrocyte count (RBC)*	|X| Mean corpuscular HGB conc. (MCHC)
|X| Platelet count*	|X| Mean corpuscular volume (MCV)
	|X| Red cell morphology

Clinical chemistry blood samples were anticoagulated with lithium heparin. Analytes determined are indicated (X) as follows:

Electrolytes:	Other
|X| Calcium*	|X| Albumin*
|X| Chloride*	|X| Blood creatinine*
| | Magnesium*	|X| Blood urea nitrogen*
|X| Phosphorous*	|X| Cholesterol* (total)
|X| Potassium*	|X| Globulins
|X| Sodium*	|X| Glucose*
Enzymes	|X| Total Bilirubin*
|X| Alkaline phosphatase	|X| Total Protein*
| | Cholinesterase	|X| Triglycerides
| | Creatinine phosphokinase*	|X| A/G ratio
|X| Lactic acid dehydrogenase	
|X| Serum alanine aminotransferase (also SGPT)*	
|X| Serum aspartate aminotransferase (also SGOT)*	

h. Necropsy was performed on all animals, and "all organs" were examined. The animals were killed by exsanguination after IP injection of sodium pentobarbitone. Tissues were fixed in 4% buffered formaldehyde, and embedded in paraffin. The 4-µm thick sections were stained with H+E. The tissues listed below were examined microscopically from rats of the control, high dose, and recovery groups: adrenals, heart, kidneys liver, lungs, spleen, testes, and gross lesions.

Organ weights were obtained for all animals necropsied at study termination, and are listed as follows: adrenals, kidneys, liver, lungs and testes.

C. RESULTS

Tabulations of the 17 measurements of particle size shows that a mean of 70.9% of the particles were in the range 0.3-1.6 µm, 13.9% in the range 1.6-3.0 µm, and 2.6% were greater than 3.0 µm.

The Study states that all rats survived and that there were no signs of toxicity. Food consumption, body weight gain, and terminal body weight are all somewhat reduced in high-dose males (compared to controls) at all measurement periods. None of these reductions is statistically significant. (See reproduced pp. 33 and 36 of the Report.) At termination the mean high-dose male body weight is 6.7% lower than control value, and the corresponding female group is 2.3% lower than control. During the 4-week recovery of the high-dose animals the food consumption shows an early, marked increase in both sexes. Body weight gain in both sexes also shows reversion to a slope comparable to that of controls. The slight body weight decrease in males during treatment at high dose is considered a compound related effect.

Ophthalmoscopic examinations were unremarkable.

Hematological data show no treatment effect at end of treatment, nor at end of recovery.

Clinical chemistry parameters at top dose in both sexes show several statistically significant effects. Thus, in males the total bilirubin is significantly decreased (relative to controls), calcium is reduced, and potassium and chloride are elevated, all at the Dunnett 5% level. In the females at top dose there are tabulations of decreased mean sodium, and increased albumin and total protein, again at the Dunnett 5% level.

Some of the electrolyte and protein alterations may reflect a tendency toward dehydration. Dose relation, however, is not apparent, and the effects were not observed in other, longer (feeding) studies. Thus, the possibility arises of an artifact, such as uncontrolled humidity. Furthermore there appears to be a "rebound effect" in some of the parameters during recovery. In summary, no compound effects appear in the data for clinical chemistry.

Terminal (eviscerated) body weight at top dose in both sexes showed a decrease (compared to controls), statistically significant in males by the Dunnett test at the 5% level. In both sexes, mainly at top dose, there are changes in O/BW ratios, which are not accompanied by histological alterations. Thus, in the males at top dose there are significantly increased O/BW ratios for lungs, liver (1% Dunnett level), and testes; while females show increased liver (1% Dunnett) and kidney ratios, again not accompanied by histological changes. Mean absolute liver weight in top-dose females is also elevated at the Dunnett 1% level. At the end of recovery the liver ratios showed a noticeable decrease in both sexes. The Reviewer interprets

the increased liver weight in top-dose females (and minimal increase in top-dose males) as a compound-related effect, possibly reversible. Strikingly elevated and dose-related liver/body weight ratios (particulararly in females) were reported in a 90-day rat feeding study on fenoxycarb (Hoffmann-LaRoche, Sept 5, 1983).

Macroscopic findings from necropsy, as tabulated in the individual animal data, show that one high-dose male presented enlarged bronchial lymph nodes, and another of the same group exhibited red foci in all lobes of the lungs.

Microscopically, the high-dose females all show either minimal or moderate nephrocalcinosis, whereas 3/5 controls show the same effect to either a minimal or slight degree. In high-dose males there was a 4/5 incidence of interstitial multifocal pneumonitis, generally slight. The corresponding controls showed the same effect in all animals.

Results from necropsy of "recovery animals" were unremarkable.

RCC PROJECT 085500
RO 13-5223/000

FC-PLOT - 1
02-SEP-87

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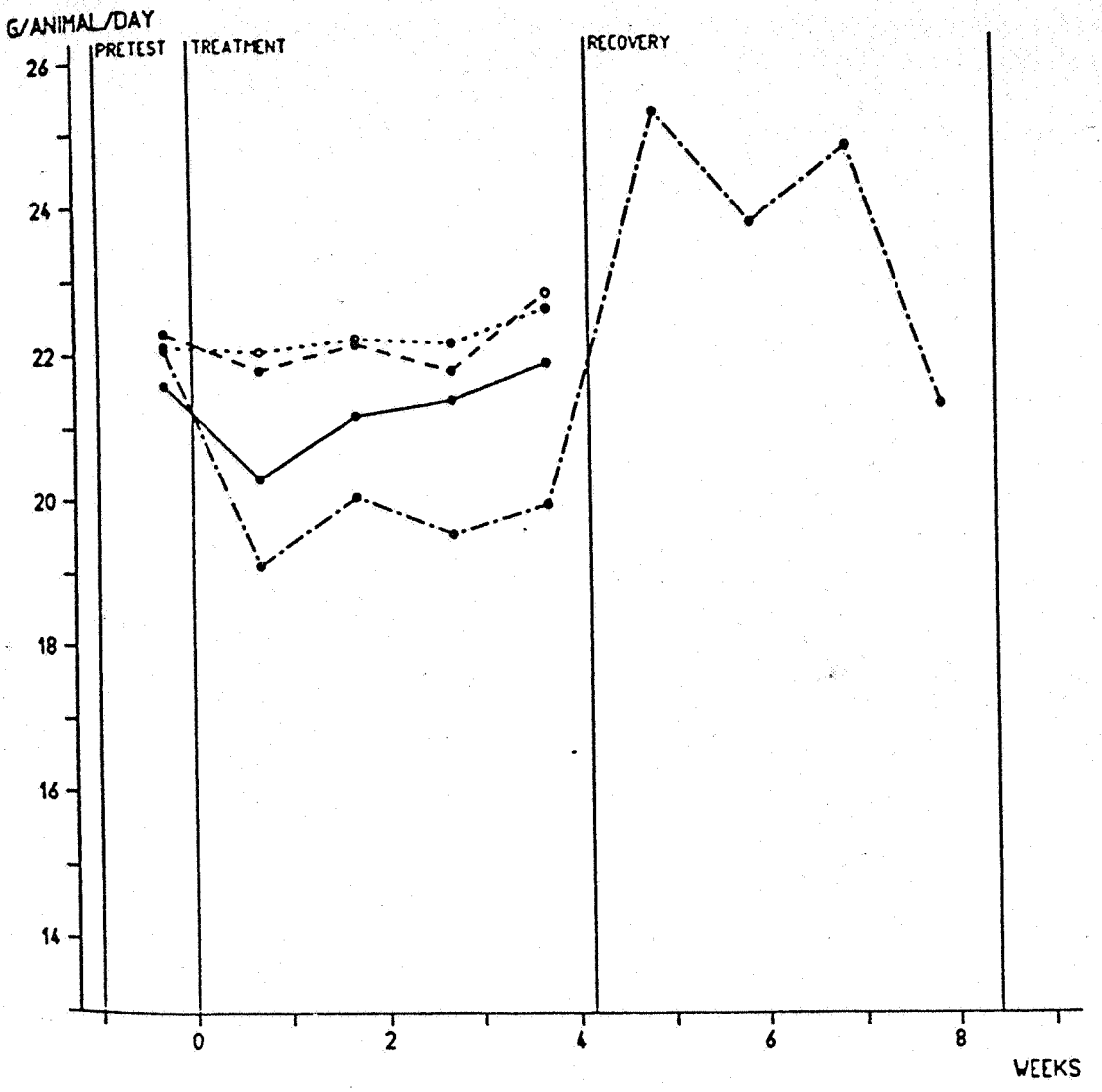
FOOD CONSUMPTION
MALES



GROUP 1 (0 MG/L)
GROUP 2 (0.01 MG/L)
GROUP 3 (0.1 MG/L)
GROUP 4 (1 MG/L)

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RCC PROJECT 085500
RO 13-5223/000

BW-PLOT - 1
02-SEP-87

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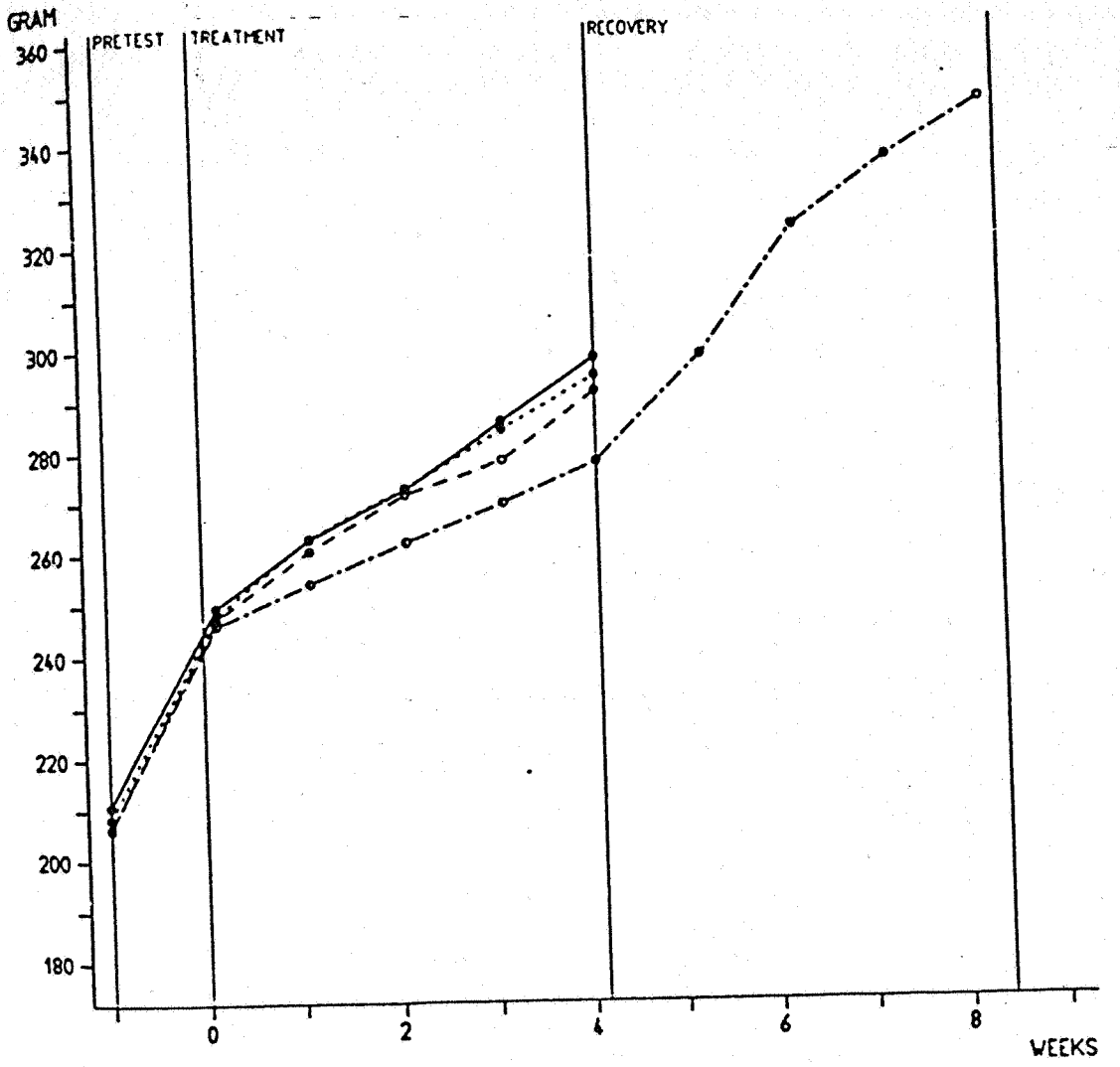
BODY WEIGHTS
MALES



——————— GROUP 1 (0 MG/L)
. . . . . GROUP 2 (0.01 MG/L)
- - - - - - - - GROUP 3 (0.1 MG/L)
—.—.—.—.— GROUP 4 (1 MG/L)