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WASHINGTON, D.C. 20460

CASWELL FILE

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MAY 30 1986

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Reviews of Studies performed on Herbicides
SC-0224 and SC-0224 4LC submitted by
Stauffer Chemical Company.
EPA ID Number: 476 EEEL/476 EEEA

TO: Robert Taylor, PM 25
Registration Division (TS-767)

FROM: Brian Dementi, Ph.D.
Review Section #1
Toxicology Branch/HED (TS-769)

Brian Dementi, 5/23/86

THRU: Robert B. Jaeger, Section Head
Review Section #1
Toxicology Branch/HED (TS-769)

*Old copy of 5-29-86
H. A. P. 5/29/86*

APPLICANT: Stauffer Chemical Company
1200 S. 47th Street
Richmond, California 94804

Stauffer Chemical Company has requested review of the accompanying studies, submitted in anticipation of a petition for the use of Herbicides SC-0224 and SC-0224 4LC. Of eight studies submitted, seven are reviewed herein. The remaining study, a teratology study (T-11050, November 5, 1992) on SC-0224 was previously submitted by Stauffer and reviewed by Toxicology Branch. See the February 8, 1984 review by Roland A. Gessert, Caswell 893C.

Summary of Results:

- 1) SC-0224 Two-Generation Reproduction Study in Rats (T-11051)
Overall Reproductive NOEL = < 150 ppm (F2B male, weanlings, relative spleen weight reduction)
Overall Clinical NOEL = 150 ppm (platelet count increase, combined male and female adult F2B generation)
Core: supplementary
- 2) Acute Inhalation Study, Rat with SC-0224 (T-11728)
LC₅₀ > 0.81 mg/L
Core = guideline
- 3) Acute Inhalation Study with SC-0224 4LC (T-11870)
LC₅₀ = 1.30 mg/L (male); LC₅₀ = 1.56 mg/L (female)
Core: guideline

- 4) Dermal Sensitization Test with SC-0224 4LC (T-11420)
NOEL = 3% SC-0224 4LC
Core: guideline
- 5) Dermal Sensitization Test with SC-0224 (T-11269)
NOEL = 3% SC-0224
Core = Guideline
- 6) Metabolism, Tissue Residue and Balance Studies of Orally Administered
[Methyl ¹⁴C] Trimethylsulfonium carboxymethylaminomethylphosphonate
(SC-0224) in Rats (PMS-148)
Quality of study acceptable
- 7) Fertility Screen with SC-0224 in Rats (T-10896)
Quality of study acceptable

Study: Dermal Sensitization Test with SC-0224 4LC

Laboratory: Richmond Toxicology Laboratory
Stauffer Chemical Company
deGuigne Technical Center
Richmond, California

Study No. and Date: T-11420, October 22, 1984

Accession No.: 258398, Appendix 4

Material Tested: SC-0224 4LC (Lot No. WCH-2304). Purity is reported to be 41.2% (p. 26).

Animals: Guinea Pigs, Male (Hartley strain)

The purpose of this study was to evaluate the potential for SC-0224 4LC to cause dermal sensitization.

Materials and Methods:

Husbandry: Standard GLP

The open epicutaneous test (OET) procedure, described in Appendix I, was followed.

This particular procedure, developed in accordance with EPA Guidelines, includes a primary irritation phase, a 26-day induction phase and two challenge phases, days 29 to 31 and 44 to 46. The material was applied topically and left uncovered.

Further details of the test procedure are quoted as follows:

"During the induction phase, the materials were applied in a volume of 100 ul to an approximate area of 2 cm². The quantities used for primary irritation and challenge phases were applied to a smaller area, 1 cm², in a volume of 25 ul. During the induction phase, each animal was exposed daily, 5 days per week for 4 weeks, to a single concentration of material. The material was applied to the right flank. Each animal was then challenged on the left flank with concurrent applications of several concentrations of the material. To minimize variations in response due to flank location, the various concentrations of test material were rotated among different application sites (Appendix II). The skin reactions were evaluated for erythema (redness) and edema (swelling) according to an 8-point scoring system (Table 2) (2). These evaluations were made 24 hours after application in the primary irritation test, at weekly intervals during induction, and daily for the 3 days following challenge and rechallenge applications."

Table 1 reproduced from the study (p. 7) summarizes the exposures the various groups of eight animals each received, including the induction challenge and rechallenge phases.

Table 1

Group	Concentrations Applied (%)		
	Induction	Challenge	Rechallenge
SC-0224 4LC			
I	10	10,3,1,d.w. ^a	10,3,1,d.w.
II	3	10,3,1,d.w.	10,3,1,d.w.
III	1	10,3,1,d.w.	10,3,1,d.w.
IV	0.3	10,3,1,d.w.	10,3,1,d.w.
V	0.1	10,3,1,d.w.	10,3,1,d.w.
VI	d.w.	10,3,1,d.w.	10,3,1,d.w.
Controls			
VII	3-HCHO ^b	1,3 HCHO d.w.	1,3 HCHO d.w.
VIII	d.w	1,3 HCHO d.w.	1,3 HCHO d.w.

^a d.w. = Distilled Water

^b HCHO = Formaldehyde

Results:

In the primary irritation study, the full strength (100%) test material produced mild irritation in all eight animals tested. At 30 percent concentration the test material produced generally somewhat milder irritation overall, but all animals were affected. Applications of 10 percent and 3 percent test material did not produce any remarkable effects (Table, p. 10).

Induction (Table, p. 11)

By day 5 there was seen a mild erythema response in 6 of 8 animals of the high-dose group. By day 12 the frequency of response declined in the high-dose group to 2/8, but the average score for the two animals was somewhat higher (2.5).

By day 19 there was erythema in the high-dose group. Lower doses of SC-0224 4LC did not elicit any remarkable effects.

Formaldehyde (3%) elicited a positive erythema response (score 1.7 to 2.3) in 6/8 animals during the 26-day induction phase.

In summary, during the induction phase, 10 percent SC-0224 4LC gave a positive skin response in terms of erythema. Lower doses were ineffective in this respect.

Challenge (Table p. 12)

When induced animals were challenged with 10 percent, 3 percent, 1 percent, 0.3 percent, 0.1 percent SC-0224 4LC and vehicle control (water), a mild erythema response (score 1.5) was seen in the high-dose group in approximately 50 percent of the animals challenged with the high dose. A milder response (score 1.0 to 1.5) was seen in the 3 percent group challenged with the high dose, and, as in the former challenge, approximately 50 percent of the animals responded. There were no other remarkable findings observed in the challenge phase. A positive response was obtained with formaldehyde.

In summary, dermal sensitization studies in which guinea pigs were induced with SC-0224 4LC and subsequently challenged with the same material it was demonstrated that animals induced by the two highest concentrations (10% and 3%) were sensitized and responded to the high concentration (10%) challenge.

Rechallenge (Table p. 13)

When induced animals were rechallenged with 10 percent, 3 percent, and 1 percent SC-0224 4LC and vehicle control (water), a response similar to that seen in the challenge study was obtained. The magnitude of response (score approximately 2) was a little higher than in the challenge, but the frequency of response was less than 50 percent.

In summary, in this dermal sensitization study it was demonstrated that animals induced by the two highest concentrations (10% and 3%) were sensitized, as evidenced by a positive response upon rechallenge with the highest concentration (10%) of those used.

Additional Comments

Appendix III (pp. 31 to 38) covering individual animal responses shows that there were no remarkable findings with respect to edema in the challenge and rechallenge studies.

Animal weight data over the 46-day trial interval revealed a tendency by the high-dose (10%) group to gain less weight. Weight gain in this group was 59.3 percent as compared to 87 percent and 72.6 percent for vehicle control groups.

Conclusions:

Results indicate that SC-0224 4LC is a mild sensitizer, with the most pronounced erythema scores observed at the high dose not exceeding 2 in the challenge and rechallenge phases of the study. As a point of definition, according to the study scoring system, a score of 2 on a scale of 0 to 4 is characterized as slight (but well-defined) erythema (pp. 8 and 17). Edema was not observed as a characteristic or complication of this study.

Conclusion: SC-0224 4LC is a mild sensitizer
NOEL = 3% SC-0224 4LC for challenge
and rechallenge.

Core: Guideline.

Study: Dermal Sensitization Test with SC-0224 Technical

Laboratory: Richmond Toxicology Laboratory
Stauffer Chemical Company
deGuigne Technical Center
Richmond, California

Study No. and Date: T-11269, October 12, 1984

Accession No.: 258398, Appendix 2

Material Tested: SC-0224 Technical (56.3%)

Animals: Guinea Pigs, Male (Hartley strain)

The purpose of this study was to evaluate the potential for SC-0224 to cause dermal sensitization.

Materials and Methods:

Husbandry: Standard GLP

The open epicutaneous test (OET) procedure, described in Appendix I, was followed.

This particular procedure, developed in accordance with EPA Guidelines, includes a primary irritation phase, a 26-day induction phase and two challenge phases, days 29 to 31 and 44 to 46. The material was applied topically and left uncovered.

Further details of the test procedure are quoted as follows:

"During the induction phase, the material was applied in a volume (liquid) or mass (petrolatum) of 100 ul or mg, respectively, to an approximate area of 2 cm². The primary irritation and challenge applications were made to smaller area, 1 cm², in a volume or mass of 25 ul or mg. During the induction phase, each animal was exposed daily, 5 days per week for 4 weeks, to a single concentration of material. The material was applied to the right flank. Each animal was then challenged with concurrent applications of several concentrations of the material applied to the left flank. To minimize variations in response due to flank location, the various concentrations of test material were rotated among different application sites. The skin reactions were evaluated for erythema (redness) and edema (swelling) according to an 8-point scoring system. These evaluations were made 24 hours after application in the primary irritation test, at weekly intervals during induction, and daily for the 3 days following challenge and rechallenge applications.

"Known sensitizers, formaldehyde and 2-mercaptobenzothiazole (2-MBT), were used as positive controls (3). Deionized water was used as the vehicle for SC-0224 Technical and formaldehyde while petrolatum (Plough, Inc.) was used as the vehicle for 2-MBT). Control and test solutions were prepared at weekly intervals. Negative control groups (animals induced with vehicle and challenged with chemical) were included for each positive control material and SC-0224 Technical. In addition, each animal served as its own control because a vehicle site was included at challenge and rechallenge.

"A group was considered to have a positive response if one or more animals exhibited an erythema score of 2 or greater. The material was considered to be a sensitizer if the challenge reaction was positive and greater than the irritation reaction. Irritation was determined from the primary irritation results and the challenge response of the appropriate vehicle group." (pp 1-2)

Table 1 reproduced from the study (p. 8) summarizes the exposures the various groups of 8 animals each received, including the induction, challenge and rechallenge phases.

Table 1

Group	Concentrations Applied (%)		
	Induction	Challenge	Rechallenge
SC-0224 Technical			
I	100	30,10,3,1,d.w. ^a	30,10,3,d.w.
II	30	30,10,3,1,d.w. ^a	30,10,3,d.w.
III	10	30,10,3,1,d.w. ^a	30,10,3,d.w.
IV	3	30,10,3,1,d.w. ^a	30,10,3,d.w.
V	1	30,10,3,1,d.w. ^a	30,10,3,d.w.
VI	0.3	30,10,3,1,d.w. ^a	30,10,3,d.w.
VII	d.w.	30,10,3,1,d.w. ^a	30,10,3,d.w.

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Table 1 (cont'd)

Controls			
VIII	1% HCHO ^b	1% HCHO, d.w.	1% HCHO, d.w.
IX	d.w.	1% HCHO, d.w.	1% HCHO, d.w.
X	3% 2-MBT ^c	3% 2-MBT, Pet	3% 2-MBT, Pet
XI	Pet ^d	3% 2-MBT, Pet	3% 2-MBT, Pet

a d.w. = Deionized Water

b HCHO = Formaldehyde

c 2-MBT = 2-Mercaptobenzothiazole

d Pet = Petrolatum

Results:

Induction (Table p. 12)

With respect to the total 26-day induction phase, it was found that by day 12 there was a positive response, in terms of erythema in all 8 animals of Group I (high dose), where the average score was 2.1. Erythema was also observed in approximately 50 percent of the Group II animals during days 12 to 26 (score 1.5 to 1.8). One animal of 8 in Group III exhibited a positive reaction. There were no responses to SC-0224 reported in any other dose groups.

Formaldehyde (1%) at days 12 to 19 elicited a positive erythema response (score 1.3 to 1.9) in 7/8 of the animals treated, with the incidence declining by day 26 to 3/8. 2-MBT (3%) yielded a response (score 2.0) in only 1 of 8 animals by day 12. Surprisingly, the vehicle for 2-MBT yielded a positive response which increased in frequency from 3/8 on day 5 to 8/8 on day 19, then decreasing to 4/8 by day 26, scores ranged 1.6 to 2.0.

In summary, during the induction phase, 100 percent and 30 percent SC-0224, 1 percent formaldehyde and petrolatum vehicle (for 2-MBT) gave positive skin responses. Responses to 10 percent SC-0224 and 3 percent 2-MBT were equivocal.

Challenge (Table, p. 13)

When induced animals were challenged with 30 percent, 10 percent, 3 percent, and 1 percent SC-0224 and vehicle control (water), a dose response for erythema was observed in

terms of frequency of response (but not magnitude which remained around 2) both as a function of challenge and induction doses. In most cases the response frequency was highest at 24 hours postchallenge, declining (exhibiting progressive decline) at the 48- and 72-hour observation times. A very definite response was seen in the formaldehyde challenge of formaldehyde induced guinea pigs. Also, it should be noted that the magnitude of the response to the vehicle (water) challenge in the formaldehyde case was surprisingly high. A meaningful challenge response was not seen in the case of 2-MBT (2%).

In summary, dermal sensitization studies in which guinea pigs were induced with SC-0224 and subsequently challenged with the same material, it was demonstrated that animals induced by the five highest doses were sensitized in a dose dependent manner and responded to challenge concentrations of SC-0224 of as low as 10 percent.

Rechallenge (Table 7)

When induced animals were rechallenged with 30 percent, 10 percent, 3 percent, and 1 percent SC-0224 and vehicle control (water), a dose response in terms of erythema (both frequency and magnitude of response) was observed as a function of the induction and rechallenge doses. In most cases, the response frequency was highest at 24-hour postrechallenge, as was true in the case of challenges. Also, as before, a very definite response was seen in the case of formaldehyde rechallenge. A striking response was not seen with 2-MBT (3%) rechallenge.

In summary, the rechallenge findings were essentially the same as those of the original challenge study, with the exception that the magnitude of the erythema response tended to decline from about 2.0 at high induction doses to 1.0 for the lower induction doses.

Additional Comments

Appendix III of the study submitted, skin response data for individual animals, shows that edema was not observed in any of the challenge or rechallenge tests, and, hence, does not constitute a positive finding in this study of SC-0224.

Weight gain of the guinea pigs over the 46-day period of study did not reveal any remarkable compound-related effects. It should be noted, perhaps, that there may have been a slight tendency for the higher dosed animals, those exposed to 30 to 100 percent test material, to gain less weight.

Conclusions:

Results indicate that SC-0224 is a mild sensitizer. The most pronounced responses, generally seen at the higher doses, were, in terms of erythema scoring, approximately 2 in the extreme case. As a point of definition, according to the study scoring system, a score of 2 on a scale of 0 to 4 is characterized as slight (but well-defined) erythema (p. 9). Edema was not observed as a characteristic or complication of this study.

The LOEL in terms of induction in the guinea pig was observed resultant to application of the 10 percent concentration sample.

In terms of response to challenge, the LOEL was 10 percent with respect to challenge concentration, eliciting a response in the group sensitized by 1 percent technical.

In terms of response to rechallenge, the LOEL was 10 percent also, but in this case with respect to the group sensitized by 10 percent technical.

Conclusion: SC-0224 is a mild sensitizer
NOEL = 3% SC-0224 for challenge and
rechallenge.

Core: Guideline.

Study: Metabolism, Tissue Residue and Balance Studies of Orally Administered [methyl ^{14}C -]trimethylsulfonium carboxymethyl amino methylphosphonate (SC-0224) in Rats.

Laboratory: Stauffer Chemical Company
Mtn. View Research Center
Pesticide Metabolism Section

Study No. and Date: Report Number PMS-148
February 4, 1985

Accession No.: 258398 (Appendix 5)

Material Tested: Analytical Grade SC-0224. (methyl ^{14}C -] trimethylsulfonium carboxymethyl amino methylphosphonate (20 mCi/mmol) was prepared by Stauffer Chemical Company.

Animals: Sprague-Dawley Rat

The purpose of this study was to evaluate the absorption, tissue distribution, and excretion of the radiolabeled SC-0224.

Methods: (As paraphrased from pages 6 to 8 of submittal)

SC-0224, ^{14}C -radiolabeled on the cation portion of the molecule (i.e., on the trimethylsulfonium portion), was administered orally to three male and three female rats at each of the doses, 35 mg/kg or 350 mg/kg. The test compound was dissolved in distilled water before administration to the animals. Urine and feces were collected at 6, 12, and 24 hours and subsequently at 24-hour intervals until termination at 120 hours. Samples of urine and feces were stored frozen.

At 120 hours into the study, rats were sacrificed by exsanguination under ether anesthesia. Tissue samples were removed, weighed and stored frozen pending combustion analysis. Tissues assayed for ^{14}C included: adrenals, bladder, blood, brain, fat (mesenteric), gonads, small intestine, large intestine, kidney, liver, lung, skeletal muscle, spleen, stomach, thymus, thyroid, heart, and hide. The remaining carcass was homogenized.

Results:

Rats showed signs of toxicity within 1 hour of administration of the high dose. The toxic signs included lethargy, ataxic movements, slow and labored breathing, salivation and occasional tremors. These signs were more noticeable in females than in males. Symptoms were markedly reduced by 12 hours following dosing.

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Within 24 hours of dosing the compound was largely excreted. By this time point, the low dose males and females had eliminated 96.3 percent and 89.1 percent, respectively, and high dose males and females had eliminated 83.9 percent and 86.1 percent, respectively. Most of the recovered dose was in the urine: low dose, male 98.5 percent, female 93.1 percent; high dose, male 94.9 percent, female 91.4 percent.

Data generated showed that the radiolabeled portion of SC-0224, trimethylsulfonium ion (TMS), was excreted essentially unmetabolized in both urine and feces.

Necropsy revealed that radiolabeled compound was distributed throughout the tissues and organs. Organs in which radiolabel was most concentrated included the following (Tables 12 to 15, pp. 29 to 32):

<u>35 mg/kg</u>		<u>350 mg/kg</u>	
<u>Male</u>	<u>Female</u>	<u>Male</u>	<u>Female</u>
Adrenals	Adrenals	Adrenals	Adrenals
Kidney	Bladder	Bladder	Bladder
Liver	Hide	Kidney	Kidneys
Thyroid		Liver	Liver
Hide		Stomach*	Stomach
		Thyroid	Thyroid

*Very high level.

When tissue residues are compared in terms of ratios of residue levels at the high to low dose and for males as compared to females, it is apparent that, firstly, a tenfold increase in dose results in more than a tenfold increase in tissue residues and, secondly, that this trend is much more pronounced in females (Table 20, p. 37). This suggests that elimination mechanisms become relatively saturated at the higher dose allowing more residue than expected to accumulate in tissues. Furthermore, this suggests that at high doses, females tend to develop higher tissue residues. This is borne out by inspection of Tables 14 to 15, pp. 31 to 32. Thus, to the extent that SC-0224 manifests toxicity in a given tissue, females would be more vulnerable as dose increases.

Conclusions:

When [methyl ¹⁴C] trimethylsulfonium carboxymethylamino-methylphosphonate is administered to rats, radiolabeled trimethylsulfonium ion is rapidly excreted, unmetabolized, in urine and feces (predominantly in urine, > 90%).

Furthermore, results show that the principal sites for localization of trimethylsulfonium ion are the adrenals, kidney, bladder, liver, thyroid, and stomach.

At high dose, elimination mechanisms appear to become saturated as evidenced by accumulation in tissues exceeding the proportionate increase in dose. This phenomenon is more pronounced in females, suggesting that as dose increases, at some dose level females will tend to begin accumulating more residue in various tissues. This would also indicate increased vulnerability of females to toxic manifestations of the cation beyond the dose at which elimination mechanisms become strained.

It should be noted that the parent compound is a water-soluble salt consisting of the trimethylsulfonium ion (cation) and the carboxymethylaminomethylphosphonate ion (anion). Only the disposition of trimethylsulfonium ion is evaluated in this study, as only this portion of the dissociable parent is labeled. A second radiolabel metabolism study in which the anionic portion of the molecule is tagged will be necessary in order to properly evaluate metabolism and distribution of the the parent molecule, SC-0224.

Quality of study acceptable



ASWELL FILE

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

004585

July 30, 1985

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM:

SUBJECT : Laboratory Data Audit. Stauffer Chemical Co. Environmental Health Center; Farmington, CT. February 19-22, 1985.

FROM : Roland A. Gessert, D.V.M.; Veterinary Medical Officer/Toxicologist

TO : John A. McCann, Director; National Laboratory Audit Program

Roland Gessert

This report provides information previously provided to the Inspector at the inspection site. While at the laboratory we ascertained that Stauffer's acute studies were conducted at their Richmond, California laboratory. Multiple dosing and inhalation toxicity studies are conducted at the Farmington, CT facility.

While we were at the laboratory, Stauffer was acquired by Chesebrough Ponds Co.

All the studies scheduled for audit were audited. These included:

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- Ro-Neet 2-year oral toxicity study in rats
- R-29148 2-year chronic toxicity/oncogenicity study in rats
- R-40244 (Racer 2-E) multi-generation reproduction study in rats
- MV-678 Teratogenicity study in New Zealand rabbits

893 C SC-0224 Teratogenicity study in CD rats

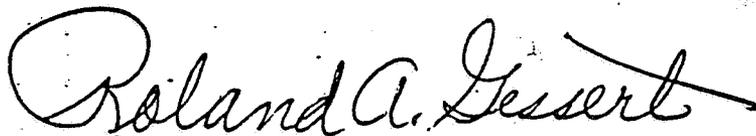
In the initial 2-year rat study with Ro-Neet, a NOEL was not demonstrated, peripheral neuromyopathy being demonstrated at all doses. (Hazleton Study 132-134. Accession # 240914). Therefore, Stauffer conducted a repeat 2-year rat study # T-10114. In the repeat study a neuropathy NOEL was demonstrated at 10 ppm and a myopathy NOEL at 60 ppm. The repeat study was Core graded Supplementary because histopathology was not done. However, these two studies combined can be graded Core Minimum or Core Guidelines. (In the one-liners, the Hazleton study is graded Core Guidelines.)

004585

In the multigeneration reproduction study of Racer 2-E (R-40244) in rats, we inquired why there was no sperm analyses for P₂ males. It is not required. Only data for 2 generations are now required, and were provided. In this study we compared testes/epidymides weights and lesions with histopathology at the high dose. Everything check O.K.

The teratogenicity study of SC-0224 in CD rats which I had reviewed, I had declared Core Supplementary data because it was not clearly stated whether doses administered were based on the 19.2% material or on the active ingredient. The data audit verified that doses were based on the active ingredient. The data for this study now are Core Minimum.

Dr. M. Adrian Gross and I worked together in auditing the Stauffer studies. Therefore, our reports should be combined for a complete audit report.



Roland A. Gessert, D.V.M.