5/16/1995

MEMORANDUM:

Subject: EPA File Symbol/EPA Reg. No.: 10356-EE
ACQ 2100 Wood Preservative Concentrate
(Sequel 2100)

From: Lucy D. Markarian, Biologist
Precautionary Review Section
Registration Support Branch
Registration Division (7505W)

LM 5/16/95

To: Cynthia Giles-Parker/James Stone, PM 22
Fungicide-Herbicide Branch
Registration Division (7505C)

Applicant: Chemical Specialties, Inc.
One Woodlawn Green
Charlotte, NC 28217

FORMULATION FROM LABEL:

Active Ingredient(s):	% by wt.
Copper Ammonium Carbonate	22.8 %
Didecyl dimethyl ammonium chloride	4.7 %
Inert Ingredient(s):	
.....	72.7 %
Total:	100.0 %

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10465-37

BACKGROUND

Chemical Specialties, Inc. Has submitted six studies in support of the registration of the product ACQ 2100 Wood Preservative Concentrate under the EPA symbol 10356-EE. The product is also known as Sequel 2100, and was tested under this name. The MRID numbers are 426682-04 through 426682-08 and 428666-01.

RECOMMENDATION

Acute dermal

It is hard to visualize how such a small amount of test material could be spread over 20 % of the body surface of the animals. (Considering 1.8 ml/ kg, a 200 g rat would be applied 0.36 ml of test material (roughly 6 drops) over a 6 X 8 cm area). Upon the placement of the gauze covering most of this could easily absorbed by the gauze. As it is, this very small amount caused very extensive damage to the skin, and it is not at all certain that the true systemic toxicity was tested. However, PRS believes that even if the test material were to be applied to 10 % of the body surface the systemic toxicity would not have been better tested, although it should have been tested that way for correct application. It was assumed by the laboratory that by spreading it over a larger area, the corrosive effect could have been bypassed. It could not have been possible due to the high pH and generally very irritating quality of the product.
The test is accepted, because repeating it will not serve any purpose, nor give the true systemic toxicity via dermal absorption.

The report does not specify the thickness of the gauze wrap. This should not be any more than 2 ply, and it should not be wrapped around the animal, but rather the site covered with gauze and held in place with tape. The trunks of the animals must be wrapped in an impermeable material. It is not certain that demiform tape qualifies as such. It is encouraged that future tests use this way of application to be acceptable.

Acute inhalation

Sprague Dawley rats weighing less than 200 grams and/or less than 8 weeks of age should not be inducted into the test. Some of the females were significantly under this weight range.

The means of measuring chamber parameters, and if they were calibrated, should be included in the report.

Eye Irritation

Eyes must be examined using white light. Hand held pen light is yellow light and should not be used. In this case this did not matter, because the test material was corrosive to the eye. PRS also recommends the use of magnification, or slit lamp.

Staining should be used starting at 24 hrs. Fluorescein after seven days is not a reliable way of determining opacity, because the eye heals from the surface inward, and when the eye starts healing will not stain. The absence of stain does not mean the absence of opacity in this case.

Dermal Irritation

The animals were wrapped in gauze binders following application. This is not a semiocclusive cover. The trunks of the animals need to be covered in an impermeable material to retard evaporation and prevent ingestion and inhalation of the test material. As is, corrosion and eschar were present at one site from 1 hr to 7 days. This is reason enough to place the irritation potential of the test material in category I, regardless of how inappropriate the binding material was.
In the presence of corrosion and eschar the erythema score for a site is always 4, yet it was graded as 1, 2, 3, but never 4. The condition of the skin after the eschar sloughed off has not been described. It is not even stated that it sloughed off, but it is assumed it did, since coloration from the product also resolved with the absence of eschar from this site only. It is doubtful that the skin returned to normal after corrosion. Additionally it is questionable that the scores of erythema were accurate as there was gray coloration from the product. Under such conditions reading of grade 1 erythema particularly is questionable as is grade one erythema with grade 1 edema.

Sensitization
The test did not define the sensitization potential of the test material.
The test appears to have been well conducted according to the Buehler protocol. The only objection is to the use of a precipitated 1 % challenge concentration, albeit claimed to be homogeneous, which may not always act as a solution. The resultant negative scores may have been due to this.

The alternative consideration is that the subject product is extremely irritating to the skin. As a result, the concentrations at which it can be tested have to be very dilute. They are dilute enough to be below the threshold where sensitization can neither be induced nor elicited. This product contains 9 1/4 % free copper. Diluting to 2 or 1 % reduces the copper concentration to 0.18 and 0.09 %, respectively. The possibility of sensitizing at these levels is pretty low, or nearly impossible as the test demonstrates. If the precipitation of the test material at 1 % is also considered, it becomes even less likely that sensitization could be induced under the given conditions.

According to the registration standard for group II copper compounds, to which the subject product belongs, all end use formulations must be labelled as sensitizers, because copper has been demonstrated to be sensitizer. Therefore, the product has to be labelled as a sensitizer. A new test need not be submitted.

LABEL

The toxicity profile of the product is:

Acute Oral.....	Category III
Acute Dermal.....	Category III
Acute Inhalation	Category III
Eye Irritation	Category I
Dermal Irritation	Category I
Sensitization	Sensitizer

The signal word is DANGER as it appears on the proposed label.

The precautionary label must be revised to read:

Corrosive. Causes irreversible eye damage and skin burns. Harmful if swallowed, absorbed through skin or inhaled. Do not get in eyes or skin or clothing. Avoid inhaling spraymist. Wear goggles or face shield, protective clothing and rubber gloves. Wash thoroughly with soap and water after handling and before eating drinking, or using tobacco. Remove contaminated clothing and wash before reuse.
Prolonged and frequently repeated skin contact may cause allergic reactions in some individuals.
The statement of practical treatment must include:

If in eyes	Call physician. Hold eyelids open and flush with a gentle steady stream of water for 15 minutes.
If on skin	Wash with plenty of soap and water. Get medical attention.
If swallowed	Call Physician or poison control center.Drink promptly a large amount of milk egg white or gelatin mixture, or if these are not available a large quantity of water. Avoid alcohol. Do not give anything by mouth or induce vomiting to an unconscious person.
If inhaled	Remove victim to fresh air. If not breathing give artificial respiration, preferably mouth to mouth. Get medical attention.

Note to Physician: Probable mucosal damage may contraindicate the use of gastric lavage.

Note to PM

Category I placement of eye and skin irritation potential necessitates the use of restricted use classification. The PM must decide if alternative labelling language is sufficient to offset the hazard and need for restricted use classification.

As the formulation appears to be an end use product, if restricted use is not implemented, then child resistant packaging must be required.

Understand Use Only
Protective clothes, gloves,
eyewear readily available
& know how to use.
No need for Restricted Use.

DATA REVIEW FOR ACUTE ORAL TOXICITY TESTING (§ 81-1)

Product Manager:21
MRID No. 426682-04
Testing Facility:WIL Research
Author(s): Gary R. Kiplinger
Species: Rat, Sprague Dawley
Age: Young Adult
Weight:207 - 266 g
Source: Charles River Breeding Laboratories, Inc.
Test Material: Sequel 2100, lot 96912, dark blue liquid
Quality Assurance (40 CFR §160.12): Included, acceptable

Reviewer: L. Markarian
Report Date:4/3/92
Report No.WIL-158014

Conclusion:

1. LD_{50} (mg/kg): **Males =** 715 (622 - 821)
   Females = 598 (504 - 710)
   Combined = 659 (572 - 759)
2. **Tox. Category:** III **Classification:**Acceptable

Procedure (Deviations from §81-1):

A range finding study determined the starting dose level of 750 mg/kg. Fasted animals were intubated with the test material as received at three dose levels. Observations were frequent on the day of treatment and daily thereafter.Body weights were recorded on day -1, at initiation and on days 7 and 14. Necropsy was performed on all animals.

Results:

Dosage mg/kg	(Number Killed/Number Tested)		
	Males	Females	Combined
500	0/5	1/5	1/10
612	1/5	3/5	4/10
750	3/5	4/5	7/10

Symptoms & Gross Necropsy Findings:

All mortality occurred within 48 hrs of intubation. Signs of toxicity included hypoactivity, salivation and yellow or red encrustation around the mouth, abnormal defecation(loose or mucoid stools), urogenital staining, ataxia, ocular discharge, and rales. Rales and urogenital staining with abnormal defecation persisted in one male and one female, respectively. All others signs of toxicity were resolved by day 6.
Necropsy of the decedents revealed signs of gastrointestinal distress, red kidneys and/or redness at the corticomedullary junction of the kidneys in the majority of the animals. This was

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observed in one of the surviving males at necropsy. Other abnormalities included red adrenals and hemorrhagic thymus in one male at 750 mg/kg. There were no other abnormalities in the survivors.

DATA REVIEW FOR ACUTE DERMAL TOXICITY TESTING (§81-2)

Product Manager:22
MRID No.: 426682-05
Testing Laboratory:WIL research
Author(s): Gary Kiplinger
Species: Rat,Sprague Dawley
Weight:218 - 287 g
Age: Young adult
Source: Charles River Breeding Laboratories, Portage, MI
Test Material: Sequel 2100, lot 96912, dark blue liquid
Quality Assurance (40 CFR §160.12): Included, acceptable

Reviewer: L. Markarian
Report Date:5/20/92
Report No.:WIL-158015

Summary:

1. **The estimated LD_{50} is** > 2000 mg/kg

3. **Tox. Category:** III **Classification:**Acceptable

Procedure (Deviation From §81-2):

The test material, as received, was applied to approximately 20 % of the body surface on clipped skin. Dosage was based on specific gravity of 1.18, equivalent to 1.8 ml/kg at 2000 mg/kg. Applications were made with a glass rod, the trunks of the animals were wrapped in gauze binders covered with Demiform tape. Collars were placed around the necks for the duration of the exposure. At 24 hrs the wrappings were removed and the sites were wiped with moist paper towels. The animals were observed frequently on the day of treatment and daily thereafter. Dermal reactions were evaluated daily. Body weights were recorded at initiation and on days 7 and 14. Necropsy was performed on all animals.

Results:

Reported Mortality

DOSAGE	(NUMBER KILLED/NUMBER TESTED)		
	Males	Females	Combined
2000 mg/kg(1.8 ml/kg)	0/5	0/5	0/10

Symptoms & Gross Necropsy Findings:
Two rats vocalized upon application of the test material. One male was hypersensitive to touch on day 3. Other observed effects as encrustation round the eyes, nose and mouth ar attributed to the collars. Six animals showed urogenital staining for 3 days. There was severe dermal irritation expressed as severe erythema, edema, blanching, atonia, gray discoloration (necrosis?), eschar, exfoliation and desquamation. Eschar persisted to the end of the study. There was a slight weight loss after the first week in four males and two females. at termination all animals showed

weight gain.
At necropsy 9/10 rats showed reddened, scabbed and thickened skin. One male had soft small testes hat was considered to be a congenital abnormality

DATA REVIEW FOR ACUTE INHALATION TOXICITY TESTING (§81-3)

Product Manager:22 **Reviewer:** L. Markarian
MRID No.: 426682-06 **Report Date:**10/1/92
Testing Laboratory: International Research and Development Corp.
Report No.:666-002
Author(s): Charles E. Ulrich
Species: Rat, Sprague Dawley
Weight: Males 252-292 g, Females 159-217 g
Age:young adult
Source: Charles River Laboratories, Inc., Kalamazoo, MI
Test Material:ACQ 2100, lot 10491, blue liquid
Quality Assurance (40 CFR §160.12): Included, acceptable
Summary:

1. **The estimated LC_{50} is:** Males 1.4(0.94 - 2.18)mg/l
   Females 2.4(1.82 - 3.25)mg/l
   Combined 1.9(1.49 - 2.43)mg/l
2. **Mean Concentration:** 5.0, 3.2, 2.2, 1.4, and 1.0 mg/l
3. **Tox. Category:** III **Classification:**Acceptable

Procedure (Deviation From §81-3):

Exposure was in a 160 l glass and steel chamber for four hours. Chamber parameters are reported to have been recorded at 30 minute intervals. The means of measuring any of these are not included. The relative humidity could not be kept within the recommended limits due to the generation system. There were five exposure levels.

The test atmosphere was generated using an atomizing assembly(Spraying Systems) with type 1/4JSS body fitted with liquid and air caps and fed by positive displacement pump. This was mounted at the top of a glass atomizer chamber. Compressed air was fed into the atomizer assembly to generate the aerosol and additional compressed air into the atomization chamber forced the aerosol out and into the exposure chamber.

Chamber concentrations were determined four times during the exposure using a modified gravimetric method to account for the loss of any volatile components. The samples were withdrawn at 2 lpm for 5-10 minutes using glass fiber filters and weighed. These were dried for 30 minutes at 50°C for 30 minutes, allowed to return to room temperature, and then reweighed. The weights were compared to a standard curve of dry versus wet filter weights.

There was only one particle size analysis per exposure level. An eight stage Andersen Cascade Impactor was used. Sampling was at 28.3 lpm for unspecified but "suitable" duration and amount.

There were daily observations and twice daily mortality checks. Body weights were recorded at initiation and on days 7 and 14. Necropsy was performed on all animals.

Results

Chamber Concentration mg/l					
gravimetric	50±1.5	3.2±0.61	2.2±0.48	1.4±0.05	1.0±0.2
MMAD ± SGD um	2.4±1.71	2.6±1.85	2.0± 2.17	2.3±1.89	2.3±1.95
Chamber					
Temperature ° C	21±0.5	22±0.5	22±0.4	22±0.5	22±0.4
Humidity %	86±4.9	82±4.7	75±0.3	66±1.5	19±3.5
Air flow lpm	67	57	67	76	67
Mortality					
Male	5/5	4/5	3/5	5/5	0/5
Female	5/5	3/5	2/5	1/5	0/5
Combined	10/10	7/10	5/10	6/10	0/10

Signs of Toxicity

Adverse reactions included labored respiration, decreased activity, salivation, and coldness to the touch. Upon removal from the chamber all animals were stained blue, and some of the animals at median levels showed abnormal gait.

Necropsy findings
At necropsy animals at 5.0 mg/l showed congested lungs. Decedents at 3.2 and 2.2 mg/kg had discoloration of the lungs. One animal at 1.4 mg/kg had red fluid in the brain. All survivors showed no abnormalities at terminal necropsy.

DATA REVIEW FOR ACUTE EYE IRRITATION TESTING (§81-4)

Product Manager:22
MRID No.:426682-07
Testing Laboratory:WIL Research
Author(s): Gary R. Kiplinger
Species: Rabbit, New Zealand White
Sex: Male
Weight:2445 g
Age: young adult
Source: Hazleton Research Products, Inc., Denver, PA
Dosage:0.1 ml
Test Material: Sequel 2100, blue liquid
Quality Assurance (40 CFR §160.12): Included, acceptable

Reviewer: L. Markarian
Report Date:4/3/92
Report No.:WIL-158017

Summary:

1. **Toxicity Category:** I

2. **Classification:**Acceptable

Procedure (Deviations From §81-4):

Undiluted test material was instilled in the conjunctival sac of one animal. Evaluations were at 1, 24, 48, 72 hrs and days 4, 7, 14, and 21 according to Draize. A hand held pen light was used as auxiliary light. Fluorescein was used to confirm corneal findings starting at 72 hrs.

Results:

Observations	(number "positive"/number tested)							
	Hour	Days						
	1	1	2	3	4	7	14	21
Cornea Opacity	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1
Iris	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1
Conjunctivae								
Redness	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1
Chemosis	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1
Discharge	1/1	1/1	1/1	1/1	1/1	/1/	1/1	1/1

Petit hemorrhage, corneal sloughing, blanching,corneal neovascularization, and corrosion of conjunctival tissue were also observed between 1 hr and 21 days.

Comments:

DATA REVIEW FOR SKIN IRRITATION TESTING (§81-5)

Product Manager:22
MRID No.:426682.1
Testing Laboratory:WIL Research
Author(s): Gary R. Kiplinger
Species: Rabbit, New Zealand White
Age:young adult
Sex:3 Male and 3 Female
Weight: 2315 - 2620 g
Dosage: 0.5 ml
Test Material: Sequel 2100, blue liquid
Quality Assurance (40 CFR §160.12): Included, Acceptable

Reviewer: L. Markarian
Report Date:4/3/92
Report No.: Wil-158016

Summary:

1. **The Primary Irritation Index =**

2. **Toxicity Category:**I

3. **Classification:**Acceptable

Procedure (Deviations From §81-5):

Undiluted test material was applied to the clipped skin of the animals with glass rod under 2 ply gauze on a 6 cm^2 area. the sites were over wrapped with gauze binders secured with Demiform tape. Collars were placed around the necks for the duration of the exposure. At 4 hrs the wrappings were removed and the sites wiped with moist paper towels. Evaluations were made at 1 hr and daily thereafter for fourteen days according to Draize.

Results:

Initially 5/6 animals showed grade 1 erythema and 1/6 grade 1 edema. 1/6 showed corrosion. Erythema intensified starting on day 3 when 2/6 showed grade 3, 3/6 grade 2, and 1/6 grade 1 erythema. the animal showing corrosion still showed corrosion on day 3. On day 4 4/6 animals showed grade 3, and 2/6 grade 2 erythema, and the site showing corrosion showed eschar. Edema was observed in 3/6 on day 6 in addition to mild to moderate erythema on day 6.. On day 7 one site still showed eschar. However no irritation except desquamation is reported at this site on day 8. Desquamation at all sites and grade 1 erythema was present at 3/6 sites at termination.

Special Comments:

DATA REVIEW FOR SKIN SENSITIZATION TESTING (§81-6)

Product Manager:22 **Reviewer:** L. Markarian
MRID No.: 428666-01 **Report Date:**7/23/93
Testing Laboratory: Product Safety Labs **Report No.:**T-2256
Author(s): Ralph Shapiro
Species: Guinea Pig, Hartley
Weight: Test 362 - 400 g, Positive Control 337 - 400 g
Age: Young adult
Source: Davidson's Mill Farm, South Brunswick, NJ
Test Material:ACQ 2100, blue liquid
Positive Control Material:DNCB
Quality Assurance (40 CFR §160.12): Included, acceptable

Method: Buehler

Summary:

1. **This Product is / is not a dermal sensitizer.**

2. **Classification:**unacceptable

Procedure (Deviation From §81-6):

Undiluted test material and eight aqueous dilutions were tested for the determination of the induction and elicitation concentrations. 100 through 5 % showed grade 3 reactions,. At 2 % 4/4 showed grade 1, 1 % showed 2/4 each of 0 and ± reactions and 0,05 % showed 3/3 negative reactions. 1 % dilution appeared to form a precipitate. The laboratory suggests that this was homogeneous and did not interfere with the test. Induction was at 2 % and elicitation at 1 %.
The positive control material was screened also for the elicitation concentration in acetone at 0.05, 0.03 and 0.01 %. 0.03 % resulted in 4 /8 ± and 4/8 0 scores, and was used for challenge. Induction was at 0.08 % in ETOH.

All applications were in Hill Top chambers in 0.4 ml aliquots. The applications were on clipped skin. The chambers were secured with adhesive tape. At 6 hrs the chambers were removed, and the sites wiped clean of any residue. There were three inductions one week apart. Challenge was two weeks after the last induction. five naive animals were used as control for each of the test and control groups.

Evaluations were at 24 and 48 hrs after each induction and challenge according to Buehler.

Results:

In the test group, during induction there were a range of responses from 0.5 to grade 2 . the reactions were somewhat more pronounced following the third induction than what was observed following the first induction. At challenge there were 2/10 ±

reactions in the test group and 2/5± reactions in the naive control group.

In the positive control test the reactions were progressively more pronounced with each subsequent induction. Following the third induction 6/10 animals showed eschar. At challenge 6/10 showed positive reactions, 4/10 showed ± reactions.

Tox Chem No: 022703 Copper Ammonium Carbonate **Current Date:** 5/16/95
069149 Didecyl dimathyl Ammonium Chloride

Laboratory: WIL Research Laboratories,Inc.,Great Lakes Chemical Co., Ashland OH
International Research & Development Corp., Mattawan, Michigan
Product Safety Labs, 725 Cranbury Road, East Brunswick, NJ 08816

S T U D Y	M A T E R I A L	MRID NO	R E S U L T S	TOX CAT	CORE GRADE
Acute Oral LD_{50} Study,Rats WIL-158014 4/3/92 WIL Research	Sequel 2100	426682-04	LD_{50} mg/kg M 715(622-821) F 598(504-710) C 659(572-759)	III	Acceptable
Acute Dermal Limit test, Rats WIL-158015 5/20/92 WIL Research	" " "	426682-05	LD_{50}> 2000 mg/kg	III	Acceptable
Acute Inhalation LC_{50} Study, Rats 666-002 10/1/92 International Research	" " "	426682-06	LC_{50} mg/l M 1.4 (0.94-2.18) F 2.4 (1.82-3.25) C 1.9 (1.49-2.43)	III	Acceptable
Eye Irritation in Rabbits WIL-158017 4/3/92 WIL Research	" " "	426682-07	Corrosive	I	Acceptable
Dermal Irritation in Rabbits WIL-158016 4/3/92 WIL Research	" " "	426682-08	Corrosion, 72 hrs	I	Acceptable

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Tox Chem No: 022703 Copper Ammonium Carbonate **Current Date:** 5/16/95
069149 Didecyl dimathyl Ammonium Chloride

Laboratory: WIL Research Laboratories,Inc.,Great Lakes Chemical Co., Ashland OH
International Research & Development Corp., Mattawan, Michigan
Product Safety Labs, 725 Cranbury Road, East Brunswick, NJ 08816

S T U D Y	M A T E R I A L	MRID NO	R E S U L T S	TOX CAT	CORE GRADE
Sensitization in Guinea Pigs T-2256 7/27/93 Product Safety	ACQ 2100 lot 031293	428666-01	sensitizer assigned according to Registration standard		unacceptable

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