EPA Reviewer: Tim McMahon, Ph.D **Signature**:
Senior Toxicologist, Antimicrobials Division (7510P) **Date**

TXR#:

DATA EVALUATION RECORD

STUDY TYPE: Skin Sensitization non-guideline (Repeat Open Application Test)

PC CODEs: 021101 **DP BARCODE:** 331024

TEST MATERIAL (PURITY): CopperShield® wood preservative

SYNONYMS: none

CITATIONS: Proctor, Deborah M.; Gujral, Jaspreet; Su, Steave (2006): Repeated Open Application Test for Allergic Contact Dermatitis due to Hexavalent Chromium [Cr(VI)] as CopperShield® : Risk Assessment for Dermal Contact with Cr(VI). Study performed by Dermatology Specialists, PSC, 444 South First Street, Louisville, KY 40202. Project number FPRL 012506. Unpublished. MRID 46884001.

Proctor, Deborah M.; Gujral, Jaspreet; Su, Steave (2006): Repeated Open Application Test for Allergic Contact Dermatitis due to Hexavalent Chromium [Cr(VI)] as Potassium Dichromate : Risk Assessment for Dermal Contact with Cr(VI). Study performed by Dermatology Specialists, PSC, 444 South First Street, Louisville, KY 40202. Project number FPRL 012406. Unpublished. MRID 46930701.

SPONSOR: Forest Products Research Laboratory, LLC, 4660 Main Street, Suite B-320, Springfield, OR 97478.

EXECUTIVE SUMMARY:

A Repeat Open Application Test (ROAT) was performed on 60 human study subjects who had been confirmed allergic to hexavalent chromium [Cr(VI)] through closed-patch testing. The purpose of this study was to develop a 10% minimum elicitation threshold

value ($MET_{10\%}$) for elicitation of allergic contact dermatitis for hexavalent chromium (as contained within the CopperShield® wood preservative treatment solution). The study design involved the application of five concentrations of hexavalent chromium (as contained within the CopperShield® wood preservative treatment solution) to the right forearm of the test subjects and application of five concentrations of potassium dichromate to the left forearm of the same subjects. Ten additional subjects not sensitive to hexavalent chromium served as controls using the highest concentration of copper contained within the wood treatment solution.

Test subjects received application of both CopperShield® treatment solution and potassium dichromate once per day for 10 days. Duration of each exposure was 6 hours after which the forearms were washed using soap provided to them. Prior to the next application, participants were evaluated for occurrence of any skin responses, including erythema, papules, pruruitis, scaling, and vesicles. Results were evaluated by Dr. Fowler, who interpreted them as either allergic or irritant in nature and graded each response. Seventy-two hours following the last testing day, participants were evaluated by Dr. Fowler to determine if an allergic contact dermatitis response had occurred. Results from the ROAT phase of the study were modeled using Benchmark Dose Software (BMDS) to fit the dose-response data and calculate the 10% Minimum Elicitation Threshold value.

Results of closed-patch testing with potassium dichromate using 12mm Finn Chambers showed that all participants for the ROAT phase of the study were confirmed to have sensitivity to hexavalent chromium. According to the report, the number of participants in the ROAT phase of the study who exhibited a high grade of ACD response (+3) was disproportionate to the North American Contact Dermatitis Group database from 1998-2002 for this grade of reaction. Twenty-six percent (26%) of the ROAT study participants showed a +3 reaction to the initial patch test, while the NACDG database of 495 individuals shows a 7.7% response percentage for a +3 reaction. Thus, to ensure that the dose-response observed in this study was representative of the hexavalent chromium-sensitized population in the United States, the dose-response in the ROAT study was extrapolated to the NACDG population by simulating the percent response expected to the ROAT if the proportions of +1, +2, and +3 responders in the current study had been consistent with that of the general U.S. hexavalent chromium-sensitized population.

In addition to normalization of the dose-response data, two scenarios were modeled from the CopperShield® results. Scenario 1 included only responses determined to be allergic in nature. Under this scenario it was assumed that if a participant reacted to a lower dose, they were allergic to all higher doses even if they did not actually react to the higher dose. Scenario 2 included both irritant and allergic responses in calculation of a 10% response level. The purpose of this scenario was to determine the effect on the 10% MET if all of the irritant responses were allergic in nature.

For Scenarios 1 and 2, the report stated that of all the models run, the unconstrained log-probit model provided the best fit for the dose-response data. For CopperShield®,

the 10% MET values for Scenarios 1 and 2 of the untransformed dose-response data were 270 and 91.8 ng Cr(VI)/cm^2 respectively, while 10% MET values for the patch-test normalized data were 349 and 166 ng Cr(VI)/cm^2 respectively. With the exception of the Scenario 2 untransformed data, these 10% MET values are higher than the previously reported value by Nethercott et al. (1994) of 89 ng Cr(VI)/cm^2 from closed patch test data. Such values may be expected on the basis that the ROAT protocol is an open application test procedure that more closely resembles real-life exposures than the closed-patch test technique.
This study is classified **acceptable/non-guideline** and fulfills the purpose for which it was conducted. However, determination of a single 10% MET value will require further discussion within the Office of Pesticide Programs.

COMPLIANCE: A signed statement of no data confidentiality claims was submitted. This study was not conducted according to Good Laboratory Practice as outlined in 40 CFR Part 160 as this was a human clinical study and GLP guidelines are not specifically applicable. A signed statement by Amy Bradley, Senior Scientist at Exponent, Inc. was included with the study report.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Materials: CopperShield®

Description: Wood preservative formulation
Lot/Batch #: Not provided
Purity: 35.46% chromic acid and 14.07% copper oxide [according to label]

CAS # of TGAI:

Concentration verified by laboratory analysis of test solutions

1. Test Materials: Potassium dichromate

Description: Stock solution obtained from Fisher Scientific Co., Houston, Texas
Lot/Batch #: Not provided
Purity: 1000 mg Cr(VI)/L

CAS # of TGAI:

Concentration verified by laboratory analysis of test solutions

According to the report (page 66), before the ROAT phase of the study, the concentration of the CopperShield® test solution preparation was verified. The stock solution was diluted to an expected concentration of 250 mg/L Cr(VI). However, colorimetric analysis showed Cr(VI) concentration to be 70 mg/L (table 7a, page 67 of the report). A repeat analysis was performed using ion chromatography because copper was suspected to have interfered with colorimetric analysis of Cr(VI) in the CopperShield® solution.

Using ion chromatography, the results of dilution gave values closer to the expected result (246 mg/L Cr(VI) identified; 250 mg/L expected).

To verify that all test solutions used during the ROAT study contained the expected amount of Cr(VI), the CopperShield® solutions and potassium dichromate solutions were analyzed for total chromium, Cr(VI), copper, and pH. Results of theses analyses, presented in Table 7c of MRID 46884001 and Table 7c of MRID 46930701, showed the measured concentration of Cr(VI) in the dose solutions to be in good agreement with the expected concentration. Tables 7b and 7c are reproduced below from the reports:

Table 7c. Results from analysis of test solutions used in Rounds 1, 2, and 3.

	Description	Total Chromium (mg/L) (mean ± S.D.)	Hexavalent Chromium (ion chromatography) (mg/L) (mean ± S.D.)	Copper (mg/L) (mean ± S.D.)	pH (std. units) (range)
1	CopperShield® solution 250 mg Cr(VI)/L, copper 153 mg/L	251 ± 17.5	258 ± 13.1	148 ± 10.2	4.9 - 5.0
2	CopperShield® solution 75 mg Cr(VI)/L, copper 45.8 mg/L	77.2 ± 3.05	76.9 ± 3.97	45.3 ± 0.78	4.9 – 5.1
3	CopperShield® solution 25 mg Cr(VI)/L, copper 15.3 mg/L	25.6 ± 0.61	25.2 ± 1.18	15.1 ± 0.40	4.9 – 5.0
4	CopperShield® solution 9 mg Cr(VI)/L, copper 5.5 mg/L	9.14 ± 0.17	9.04 ± 0.21	5.36 ± 0.14	4.9 – 5.0

Data copied without alteration from page 68 of MRID 46884001.

Table 7c. Results from analysis of test solutions used in Rounds 1, 2, and 3

	Description	Total Chromium (mg/L) (mean ± S.D.)	Hexavalent Chromium (ion chromatography) (mg/L) (mean ± S.D.)	pH (std. units) (range)
1	Potassium dichromate solution 250 mg Cr(VI)/L	245 ± 11.8	245 ± 7.55	7.0
2	Potassium dichromate solution 75 mg Cr(VI)/L	74.7 ± 1.55	72.8 ± 3.20	6.8 – 7.0
3	Potassium dichromate solution 25 mg Cr(VI)/L	24.5 ± 0.81	23.9 ± 1.44	6.7 – 6.9
4	Potassium dichromate solution 9 mg Cr(VI)/L	8.96 ± 0.85	8.65 ± 0.99	6.6 – 6.8

Data copied without alteration from page 64 of MRID 46930701.

2. Vehicle and/or positive control: Deionized water containing 153 mg/L copper chloride (the concentration of copper in the highest dose tested in the ROAT study) was used as a control solution in this study as part of the ROAT protocol.

B. STUDY DESIGN and METHODS:

The objective of the present study was to develop a 10% Minimum Elicitation Threshold value (MET_{10}) for hexavalent chromium (CrVI) as contained within the ACC wood treatment solution in previously sensitized individuals. The results of this experiment would provide a value for determining a level of exposure to hexavalent chromium as contained within the ACC treatment solution considered protective for elicitation of allergic contact dermatitis. An additional concurrent experiment was also conducted using potassium dichromate for purposes of providing data for assessing risk from exposure to hexavalent chromium in environmental media such as contaminated soil. The ROAT study is designed to represent more realistic dermal exposures that might occur to potential dermal sensitizers and potential allergic contact dermatitis reactions in people (i.e. repeated, non-occluded exposures).

Study Participants

A two-stage strategy was used to identify study participants for this study according to the report (page 36). A list of potentially eligible participants was first compiled from the patient population of Dr. Joseph Fowler's private medical practice (Dermatology Specialists, PSC). Second, a research assistant who did not work in the clinic contacted individuals on this list by telephone to determine willingness to participate in this study and to verify that they met the inclusion and exclusion criteria described in this report

Inclusion criteria included age over 18 years, English speaking, able and willing to travel to the dermatology clinic for all visits, and known chromium sensitization status. *Exclusion criteria* included current exposure to chromium or copper in the workplace or home, active eczematous allergic contact dermatitis, fissures or lesions of the skin, serious systemic disease or medical condition, current use of immunosuppressive drugs, pregnancy or attempting pregnancy, current breast feeding, illicit drug or alcohol use, and plans to leave the area for 2 days or more.

A total of 148 individuals who had demonstrated a positive reaction to Cr(VI) in previous patch tests were contacted by the study research assistants.
Of these, 88 were found eligible and agreed to come for an initial visit to the clinic.

In addition to the above, 12 individuals who were not known to be sensitive to Cr(VI) were identified among the employees, former employees, and relatives of employees of Dr. Fowler to participate as part of the non-sensitized population.

Initial Clinic Visit

For individuals who were determined to be eligible and who were interested in

participating in the study, the research staff scheduled an initial visit to the research facility at the clinic. If consent was given to participate in the study at the clinic on the initial visit, a patch test was performed to confirm sensitivity to CrVI.

The initial visit to the clinic included a brief questionnaire given to potential participants regarding occupational and medical history relevant to the conduct of the study. Potential participants were also examined by Dr. Fowler for presence of any skin disease. Participants were asked to refrain from activities during the study period that could irritate the test sites and also instructed to avoid contact with anything to which they are known to be allergic. Participants were instructed not to use topical steroids or other treatments in the test areas starting one week before the test, during patch-testing days, and during the two-week ROAT study period.

IRB Approval and Informed Consent

Informed consent forms were given to study participants and they were allowed to decide whether to participate in the study. Consent procedures were approved by Schulman Associates Institutional Review Board (SAIRB).

Patch Testing

Patch testing was conducted using 12 mm Finn Chambers to verify that participants were Cr(VI)-sensitive. Potassium dichromate (0.25%) was used in a 12mm Finn Chamber applied to an area of skin on the upper back. The loaded chamber was secluded with Scanpor® tape to expose an area of approximately 1 cm^2. The actual concentration of potassium dichromate applied to the Finn Chamber was not stated in the report. Depending on the volume of the solution applied to the test patch, this dose could vary. Typically, a 10 or 20 microliter volume is used for Finn Chamber testing. If this is the case, then, knowing that a 0.25% solution was used, the dose could be in the range of 25-50 micrograms applied to the 1 cm^2 area of the skin.
Participants who were thought to be CrVI sensitive on the basis of previous patch tests but who were negative in the current patch test procedure were excluded from participation in the ROAT study. Those thought to be non-sensitized but who showed a positive reaction in the patch test were asked if they were interested in participating in the ROAT as a member of the sensitized group.

According to the report (page 61), eighty-eight patch tests were performed on participants who were thought to be sensitive to CrVI in the past, and 12 participants who were not known to be allergic to CrVI. Of the 88 participants, 62, or 70%, had a positive reaction to the patch test. One individual who had a positive reaction did not continue into the ROAT phase of the study based on the presence of active dermatitis at the time of the ROAT phase. Three other participants had scheduling conflicts and chose not to participate in the ROAT phase. Thus, in the end, 58 individuals with previous positive patch tests for CrVI were included in the ROAT phase of the study. This group consisted of 25 men and 35 women

Of the 12 tested that were thought to be non-sensitized, ten of these participants had negative reactions and were included on the control population for this study. This population consisted of women only. The two who tested positive for CrVI sensitivity agreed to participate in the ROAT study as part of the test group.

Those individuals who consented to participate in the study were patch tested, as noted above. This involved three visits to the clinic. On the first visit, the patch was applied; on the second visit (approximately 48 hours after application), the patch was removed; on the third visit (another 48 hours) the patch test was read.

Dose levels for ROAT exposures

As stated above, 60 participants who were determined to be CrVI-sensitive and 10 who were not CrVI-sensitive participated in the ROAT study.

Doses used in the ROAT phase of the study were 0, 90, 250, 750, and 2500 ng/cm^2. According to the report, the lowest non-zero concentration tested in this study represents the MET_{10} from the study of Nethercott et al. (Occup. Environ. Med 51: 371-380, 1994) and was the concentration used by EPA in determining the level of concern for dermal contact with CrVI in articles that may contain CrVI. The top concentration used in the present study represents, according to the report, the concentration of CrVI on CopperShield® treated wood immediately following treatment and is considered the extreme upper-bound of possible exposures to CrVI from exposure to CopperShield® treated wood.

A schematic of the application sites and chemicals applied was shown on page 51 of the study report. A flexible transparent plastic template (consisting of five 1 cm^2 cut outs arranged linearly and spaced 2 cm apart) was used as a guide to administering the test substances on the forearms. Study participants were blinded to the control and test solutions being applied. Ten microliters of each test solution was applied with a micropipette in the 1 cm^2 square areas marked on the forearms. The two highest doses were tested at opposite ends of the template to reduce the possibility of "excited skin syndrome." The vehicle/control solution was applied in the middle of the template. After application, the test solutions on the forearms were dried using a hair blow-dryer. According to the report, this procedure had no effect on the applied dose based on the statement that CrVI is non-volatile.

Exposure time for each application in the ROAT study was six hours to both the CopperShield® solutions and to the potassium dichromate solutions. After the six hour exposure, participants washed their forearms using soap provided to them. This was apparently not done at the clinic, based on the statement in the report that "Each day when they came in for testing, they were reminded to wash off the test solutions. At the subsequent study visit, each participant was asked to recall the time when they washed

their forearms and this was recorded in their study file." (page 51 of MRID 46884001).

Participants received a total of 10 applications of all test solutions (five times per week, Monday through Friday, for two weeks). Participants were divided into three groups, or 'rounds' according to the report (page 52). Round one consisted of 25 participants (22 Cr-sensitive and 3 controls). Round two consisted of 31 participants (26 Cr-sensitive and 5 controls). Round three consisted of 14 participants (12 Cr-sensitized and 2 controls). The three rounds were stated to be identical in terms of procedures conducted and methods used, with the exception of the soap used to wash the test sites in Round 1 vs. Rounds 2 and 3.

RESULTS

Interpretation of allergic and irritant responses

On each day of testing, prior to application of the test solution for that day, skin responses were evaluated. Evaluation was made for presence of allergic contact dermatitis as well as irritant responses.

If the response was determined to be allergic, the challenge to that dose was discontinued. If the response was considered irritant or uncertain, dosing was continued to aid in the interpretation. Dosing was discontinued only for the dose to which an individual experienced an allergic response.

Seventy-two hours after the last testing day, participants were evaluated by Dr. Fowler to determine the presence of an ACD response. All skin responses were graded for erythema, vesicle formation, papule, scaling, and prurutis, The grading of each of these was performed using the following criteria (Table 3 of the report, page 54 of MRID 46884001):

Table 3. Grading criteria for the symptoms of allergic and irritant responses

Symptom/Sign		Grade
Morphological		
Erythema (redness)	0	No Erythema
	1+	Mild erythema
	2+	Moderate erythema
	3+	Severe erythema
Vesiculation	0	No vesicles
	1+	Occasional vesicles
	2+	Extensive vesiculation
	3+	Bullae formation
Papules	0	No papules
	1+	Occasional papules
	2+	Many papules
	3+	Extensive papules
Scaling	0	No scaling
	1+	Mild scaling
	2+	Moderate scaling
	3+	Extensive scaling
Subjective		
Pruritus (itching)	0	No itching sensation
	1+	Mild sensation
	2+	Moderate sensation
	3+	Strong sensation

Note:

Bulla	-	fluid-filled raised area greater than 5 mm in diameter; a large blister
Erythema	-	a term used for redness of skin produced by congestion of capillaries
Papule	-	elevated solid area less than 5 mm in diameter
Pruritus	-	itching; an uncomfortable cutaneous sensation that provokes the desire to rub or scratch the skin to obtain relief
Scaling	-	dry, horny, plate like excrescence, usually the result of imperfect cornification
Vesicle	-	a small epidermal elevation, less than 5 mm in diameter, usually containing a clear fluid; a small blister

Data copied without alteration from page 54 of MRID 46884001.

Results of Patch Testing

A summary of the responses to patch testing for determination of Cr-sensitivity and individual responses to the ROAT study is shown in the following table (Table 8, from pages 70-72 of MRID 46884001).

Table 8. Day of allergic responses from ROAT for CopperShield® challenge for each participant

Participant #[a]	Patch-Test Grade	Dose CopperShield® (ng Cr(VI)/cm^2) 0	90	250	750	2,500
Controls						
60	No reaction	--	--	--	--	--
61	"	--	--	--	--	--
62	"	--	--	--	--	--
63	"	--	--	--	--	--
92	"	--	--	--	--	--
93	"	--	--	--	--	--
94	"	--	--	--	--	--
95	"	--	--	--	--	--
96	"	--	--	--	--	--
97	"	--	--	--	--	--
No. of control participants reacting to any dose =		0	0	0	0	0
Cr(VI)-sensitized						
4	1+	--	--	--	--	--
9	1+	--	--	--	--	--
10	1+	--	--	--	--	day 10
12	1+	--	--	--	--	--
14	1+	--	--	--	--	--
15	1+	--	--	--	--	--
16	1+	--	--	--	--	--
28	1+	--	--	--	--	--
29	1+	--	--	--	--	--
30	1+	--	--	--	--	--
35	1+	--	--	--	--	--
37	1+	--	--	--	--	--
39	1+	--	--	--	--	--
43	1+	--	--	--	--	--
45	1+	--	--	--	--	--
46	1+	--	--	--	--	--
47	1+	--	--	--	--	--
48	1+	--	--	--	--	--
50	1+	--	--	--	--	--
51	1+	--	--	--	--	--
52	1+	--	--	--	--	--
53	1+	--	--	--	--	--
55	1+	--	--	--	--	--

[a] Participants organized by patch-test grade

In

Participant #[a]	Patch-Test Grade	Dose CopperShield® (ng Cr(VI)/cm^2) 0	90	250	750	2,500
64	1+	--	--	--	--	--
67	1+	--	--	--	--	--
73	1+	--	--	--	--	--
74	1+	--	--	--	--	--
78	1+	--	--	--	--	--
90	1+	--	--	--	--	--
91	1+	--	--	--	--	--
98	1+	--	--	--	--	--
99	1+	--	--	--	--	--
100	1+	--	--	--	--	--
No. of 1+ participants reacting to a dose =		0	0	0	0	1
3	2+	--	--	day 16	--	day 16
8	2+	--	--	day 10	day 11	day 5
11	2+	--	--	--	--	--
18	2+	--	--	day 15	day 11	day 8
49	2+	--	--	--	day 12	day 10
68	2+	--	--	--	--	--
76	2+	--	--	--	--	--
79	2+	--	--	day 12	day 8	day 9
80	2+	--	--	--	--	--
81	2+	--	--	--	--	--
82	2+	--	--	--	--	day 12
No. of 2+ participants reacting to a dose =		0	0	4	4	6
1	3+	--	--	--	--	day 9
2	3+	--	--	--	day 10	day 8
5	3+	--	--	--	--	--
7	3+	--	--	--	--	day 16
24	3+	--	--	--	--	--
38	3+	--	--	day 15	day 12	day 8
44	3+	--	--	--	day 9	day 11
54	3+	--	--	--	--	--
57	3+	--	--	--	--	--
58	3+	--	--	--	day 5	day 8
65	3+	--	--	--	--	day 15
66	3+	--	--	--	--	--
70	3+	--	day 5	day 5	day 2	day 2
75	3+	--	--	--	--	day 12
85	3+	--	day 11	day 10	day 9	day 5
86	3+	--	--	--	--	--

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In addition to these data, the study authors were interested in determining whether the 10% MET from the study population in this report were representative of the Cr(VI)-sensitized population in the United States. To determine this, the number of participants with a +1, +2, or +3 patch-test reaction were compared to the proportions of individuals with these same patch test grades in the NACDG database of patch-test grades for all individuals patch tested by NACDG physicians from 1998 through 2002.

The number of participants in each patch-test grade and dose group was extrapolated (scaled up or down) depending on the relative proportion of the total number of people in each of the three patch-test grades. The data from the patch-test normalized population were the used for estimating the 10% MET values that are representative of the general Cr(VI)-sensitized population in the United States.

A corollary to this determination was finding out if the results of prior patch-testing on the study population, which was performed using 8-mm Finn chambers, was comparable to the 12-mm chambers that were used to make the current determination of sensitivity to Cr(VI) in the same study population. As discussed in Nethercott et al. (1994), it has been suggested that a sub-MET concentration could induce a sensitization response based on an increase in surface area of the patch due to greater systemic uptake of the chemical. Although shown not to be the case from experimentation done in the Nethercott et al. study, the current investigation also looked into this possibility. These data are summarized in Table 6 of the report, pages 64-65 of MRID 46884001 and are shown below:

Table 6. Potential sources of sensitization to Cr(VI) among the study participants

				Patch-Test Grade			Possible Source of Cr(VI)-Sensitization					
Participant No.	Age (years)	Sex	Race	Previous 8-mm Patch	Year of 8-mm Patch	12-mm Patch (2005)	Cement	Leather	Wood	Cosmetic	Other	Unknown
1	21	F	C	☒	☒	3+		✓				
2	62	M	C	2+	2005	3+		✓				
3	59	M	C	2+	2002	2+						✓
4	63	F	C	2+	2001	1+						✓
5	52	F	C	3+	2003	3+					✓	
7	37	F	C	3+	2002	3+						✓
8	50	M	C	2+	2001	2+	✓					
9	35	M	AA	2+	2005	1+						✓
10	41	F	AA	1+	2005	1+						✓
11	37	M	C	2+	2004	2+			✓			
12	34	F	C	1+	2005	1+				✓		
14	76	F	C	1+	2005	1+					✓	
15	58	F	C	1+	2004	1+						✓
16	20	M	AA	1+	2005	1+		✓				
18	48	M	C	1+	2004	2+		✓				
24	75	M	C	1+	2004	3+						✓
28	46	F	C	1+	2005	1+						✓
29	49	M	C	2+	2002	1+					✓	
30	64	M	C	1+	2001	1+		✓				
35	39	M	C	1+	2003	1+		✓				
37	56	F	C	1+	2004	1+						✓
38	38	F	C	2+	1997	3+		✓				
39	42	F	C	1+	2005	1+						✓
43	47	F	C	1+	1991	1+		✓				
44	84	M	C	1+	1992	3+	✓		✓			
45	64	F	C	1+	1989	1+				✓		
46	51	F	C	1+	2005	1+						✓
47	25	F	AA	1+	2005	1+						✓
48	63	F	C	1+	1990	1+		✓				
49	51	F	C	1+	1990	2+					✓	

Participant No.	Age (years)	Sex	Race	Patch-Test Grade: Previous 8-mm Patch	Patch-Test Grade: Year of 8-mm Patch	Patch-Test Grade: 12-mm Patch (2005)	Possible Source of Cr(VI)-Sensitization: Cement	Leather	Wood	Cosmetic	Other	Unknown
50	71	M	AA	1+	2004	1+					✓	
51	57	F	C	1+	2004	1+						✓
52	47	M	C	1+	2001	1+			✓			
53	50	M	C	1+	2003	1+	✓					
54	59	F	C	2+	1991	3+				✓		
55	43	F	C	1+	2005	1+						✓
57	40	M	C	3+	2003	3+		✓			✓	
58	49	M	C	1+	1992	3+	✓					
64	54	M	C	1+	2001	1+			✓			
65	54	F	AA	2+	1998	3+		✓				
66	56	F	C	1+	2003	3+						✓
67	52	F	C	1+	2002	1+				✓		
68	58	F	C	1+	2004	2+						✓
70	39	M	C	3+	1992	3+	✓					
73	50	F	C	1+	2003	1+						✓
74	42	F	C	1+	2001	1+	✓					
75	41	F	C	3+	1998	3+						✓
76	23	M	C	2+	2003	2+		✓				
78	42	M	C	1+	1993	1+						✓
79	51	M	C	2+	1997	2+	✓					
80	62	M	C	2+	2005	2+						✓
81	57	F	C	1+	2005	2+					✓	
82	29	M	C	1+	2004	2+					✓	
85	28	F	C	3+	2002	3+		✓				
86	53	F	AA	1+	1990	3+						✓
90	30	F	C	☒	☒	1+						✓
91	42	M	C	1+	2001	1+			✓			
98	50	F	C	1+	2005	1+				✓		
99	45	F	C	1+	2005	1+				✓		
100	70	F	C	1+	2005	1+			✓			

Note: AA - African American; C - Caucasian; F - female; M - male

The table shows (and as discussed in the report), that 41 of the 58 test subjects, or 71%, had the same patch test grade with the 8-mm and 12-mm patch. Fourteen subjects had a higher test grade with the 12-mm patch than the 8-mm patch, and 3 subjects had a lower patch test grade with the 12-mm patch than the 8-mm patch. The report also stated (page 59) that there were 26 participants who tested positive with the 8-mm patch but did not have a positive response with the 12-mm patch in this study. It is assumed from examining the data in Table 6 that these were subjects who eventually did not participate in the ROAT phase of the study as shown in Table 8.

Results of ROAT

Summary dose-response data for the ROAT phase of the study were presented in Table 12, page 95 of MRID 46884001 for the CopperShield® treatment solution and on page 89 of MRID 46930701 for potassium dichromate. Individual reactions were presented in Tables 10 and 11, pages 90-94 of MRID 46884001 and Tables 10 and 11, pages 85-88 of MRID 46930701. It is to be noted that the statement was made in MRID 46884001 (page 69) that "participants who had a higher grade of reaction (2+ and 3+) on the initial patch test were far more likely to develop an allergic response during the ROAT." It would not be known what the initial induction dose of CR(VI) was for the study participants nor what elicitation doses these participants would have received over the years. Thus, the relationship between the patch test data and the results of the ROAT could not be examined further. It is known from previous experimental work in animals (Scott et al., 2002) that doses required for both induction and elicitation are dose-responsive in nature, that is, elicitation doses can be affected by the induction dose and vice-versa.

The summary table notes responses interpreted under two scenarios. Scenario 1 included responses determined only to be allergic in nature, while Scenario 2 included both allergic and irritant responses combined.

Table 12. Dose response for the two scenarios evaluated for $MET_{10\%}$

Dose (ng Cr(VI)/cm^2)				
0	90	250	750	2500
Number of Participants				
60	60	60	60	60
Actual Responses				
0 (0%)	2 (3%)	7 (12%)	10 (17%)	17 (28%)
Scenario 1 Responses				
0 (0%)	2 (3%)	7 (12%)	11 (18%)	17 (28%)
Scenario 2 Responses				
0 (0%)	4 (7%)	12 (20%)	18 (30%)	22 (37%)

Data reproduced unaltered from page 95 of MRID 46884001 for the CopperShield® treatment solution.

Table 12. Dose response for the two scenarios evaluated for $MET_{10\%}$

Dose [ng Cr(VI)/cm^2]				
0	90	250	750	2500
Number of Participants				
60	60	60	60	60
Actual Allergic Responses				
0	5	8	11	19
(0%)	(8%)	(13%)	(18%)	(32%)
Scenario 1 Responses				
0	5	9	13	20
(0%)	(8%)	(15%)	(22%)	(33%)
Scenario 2 Responses				
0	6	10	16	23
(0%)	(10%)	(17%)	(27%)	(38%)

Data copied unaltered from MRID 46930701 for potassium dichromate.

Dose-Response Modeling and Calculation of 10% Minimum Elicitation Threshold

Two scenarios were modeled with respect to calculation of the 10% MET in both studies. Dose-response modeling in both cases was done following the USEPA benchmark dose approach and using the Benchmark Dose Software distributed by EPA.

In the first scenario, the statistical analysis included all allergic responses. While in the second scenario, the statistical analysis included both allergic and irritant responses; that is, the assumption in the second scenario was that all visible irritant responses were allergic in nature. The equations used for patch–test normalization for both Scenario 1 and 2 are given in Appendix F, pages 322-324 of the report.

The summary data on page 95 of MRID 46884001 show the dose-response for the

various concentrations of CopperShield® applied to the skin in the ROAT phase of the study. For Scenario 1, the point closest to the 10% response level was the 250 ng/cm^2 concentration of Cr(VI), [response of 12%], while modeling of this result predicted a 9.6% response. From the best fitting model for Scenario 1 (allergic responses only), a value of 270 ng/cm^2 concentration of Cr(VI) is determined.

For Scenario 2 [allergic and irritant responses combined], the data point closest to the 10% response level was the 90 ng/cm^2 concentration of Cr(VI) from the study (7% response). The modeled 10% response would be 91.8 ng/cm^2 concentration of Cr(VI)

Summary data on page 89 of MRID 46930701 for potassium dichromate and modeling results on page 92 of this same report show that for Scenario 1, the point closest to the 10% response level was the 90 ng/cm^2 concentration of potassium dichromate [response of 8%], while modeling predicted an 8.7% response. From the best fitting model for Scenario 1, a value of 118 ng/cm^2 was determined as the 10% MET.

For Scenario 2 in MRID 46930701, which included both irritant and allergic responses, page 89 of the report showed the 90 ng/cm^2 concentration as the 10% response level. The model predicted a 10.2% response at this concentration. From the bet fitting model, the 10% MET value for Scenario 2 was determined to be 86.6 ng/cm^2 for potassium dichromate.

Extrapolation of Study Results to NACDG Cr(VI)–Sensitized Population

Details of the process used to extrapolate results from the present study to the NACDG clinical population were discussed on page 101 of the study report. Table 15 reproduced below from the report shows comparison of the patch-test grades in this study with the NACDG (North American Contact Dermatitis Group) database. As compared to the NACDG database, there appeared to be a higher proportion of subjects in the present study with a +3 reaction to patch testing (26.7%) as compared to the NACDG clinical database (7.7%), and a lower percentage of responses at the +1 and +2 reaction levels.

Table 15. Comparison of the grades of patch-test responses in study participants with those of the Cr(VI)-sensitized population in the North American Contact Dermatitis Group database 1998–2002

	Grade of Patch-Test Reaction			
	1+	2+	3+	Total
Number of participants in each group in the initial patch test	33	11	16	60
Proportion of participants in each group in the initial patch test	55%	18.3%	26.7%	100%
Number of participants in each group in the NACDG database 1998–2002	312	145	38	495
Proportion of participants in each group in the NACDG database 1998–2002 (%)	63%	29.3%	7.7%	100%

Data copied unaltered from page 101 of MRID 46884001.

From the data presented in this table, it is observed that the proportion of participants showing a +3 reaction in the patch test was considerably higher than the proportion of participants showing a +3 reaction from the NACDG database. To ensure that the dose-response observed in this study was representative of the chromium-sensitized population in the United States, results from the present ROAT study were extrapolated to the NACDG database as described on page 96 of MRID 46930701 and page 102 of MRID 46884001.

Calculated values for the 10% MET for both the original data and the normalized data are shown in the following table from page 108 of MRID 46884001 and page 103 of MRID 46930701.

Table 19. $MET_{10\%}$ calculated for Scenarios 1 and 2 from the present study and the patch-test-normalized populations

Population	Scenario[a]	Modeled $MET_{10\%}$ [ng Cr(VI)/cm^2]
Present study population	1	270
Patch-test-normalized population	1	349
Present study population	2	91.8
Patch-test-normalized population	2	166

[a] Scenario 1 included only allergic responses, Scenario 2 included both allergic and irritant responses.

Data copied unaltered from page 108 of MRID 46884001.

When normalized to the U.S. population (on the basis of the NACDG database of 495 individuals from 1998-2002), the resulting 10% MET values of 349 ng/cm^2 and 166 ng/cm^2 for Scenario 1 and 2 respectively are higher than the 10% MET values of 270 ng/cm^2 and 91.8 ng/cm^2 that were derived from the dose-response data set prior to normalization of the data.

Table 19. $MET_{10\%}$ calculated for Scenarios 1 and 2 from the present study and the patch-test-normalized populations

Population	Scenario[a]	Modeled $MET_{10\%}$ [ng Cr(VI)/cm^2]
Present study population	1	118
Patch-test-normalized population	1	364
Present study population	2	86.6
Patch-test-normalized population	2	269

[a] Scenario 1 includes allergic responses only; Scenario 2 includes both allergic and irritant responses.

Data copied unaltered from page 103 of MRID 46930701.

Calculated 10% MET values for scenarios 1 and 2 using the original dose-response data show values of 118 and 86.6 ng/cm^2 for potassium dichromate. When normalized to the U.S. population (on the basis of the NACDG database of 495 individuals from 1998-2002), the resulting 10% MET values are 364 ng/cm^2 and 269 ng/cm^2 for Scenario 1 and 2 respectively.
It is of interest that the 10% MET value obtained from the non-normalized dose-response data in the study with potassium dichromate (118 ng Cr(VI)/cm^2) is approximately 30% higher than the 10% MET value derived from the Nethercott et al. (1994) study (89 ng Cr(VI)/cm^2). The closeness of these two values from different studies suggests that for potent dermal sensitizers, results from open or closed tests may not differ significantly, and also suggests that for both the Nethercott et al. study and the present study, the test population may have been composed of persons more sensitive to Cr(VI) than the general Cr-sensitive population.

E. REVIEWER'S CONCLUSIONS:

The current submitted study was designed to obtain a 10% Minimum Elicitation Threshold value (or 10% MET) from subjects known to be sensitive to Cr(VI) employing the Repeat Open Application Test protocol. From the FIFRA Science Advisory Panel review of this issue in May of 2004, it was suggested that such a test would provide a more realistic basis for conducting a risk assessment of dermal sensitization risk from contact with treated wood containing Cr(VI). Previously, the Agency relied upon the study of Nethercott et al, (1994) in which a 'sensitization reference dose' of 9 ng/cm^2 was derived from a 10% MET value of 89 ng Cr(VI)/cm^2. An uncertainty factor of 10 was applied to the 10% MET from the Nethercott et al. study to account for lack of data on human variability in the dermal sensitization response to Cr(VI), especially from repeated dermal contact. It is known that repeated contact with dermal sensitizers can lower the concentration subsequently needed to cause an elicitation of allergic contact dermatitis, and the Nethercott study was based on a single dermal exposure.

The present study utilized a study population of 60 human subjects who were exposed to various concentrations of Cr(VI) once a day over a period of 10 days using the ROAT protocol. Exposure was to Cr(VI) both as contained within the CopperShield® wood preservative treatment solution and as potassium dichromate. Values from these two experiments are intended for different applications. The 10% MET value obtained from study of the CopperShield® wood treatment solution is for determination of a 'safe' area dose for protection against elicitation of allergic contact dermatitis that could occur from contact with the treated wood. The 10% MET value obtained from study of potassium dichromate is for application to environmental cleanup, for example, soil contaminated with Cr(VI). It is noted that both test materials were examined concurrently on the same subjects.

The study participants were first confirmed to be Cr(VI) sensitive through patch testing

using 12mm Finn Chambers. The participants also had a previous history of testing for Cr(VI) sensitivity and the results of these previous tests were compared to the current patch testing. Comparison of the results of the previous patch testing with the current patch test showed that 41 of the 58 test subjects, or 71%, had the same patch test grade with the 8-mm and 12-mm patch. Fourteen subjects had a higher test grade with the 12-mm patch than the 8-mm patch, and 3 subjects had a lower patch test grade with the 12-mm patch than the 8-mm patch. The results of the ROAT test showed that participants who had an initial patch test grade that was 2+ or 3+ also appeared more likely to show allergic contact dermatitis reactions in the ROAT phase and at lower concentrations (Table 8 of MRID 46884001).

The patch test results also showed what appeared to be a disproportionate percentage of participants who had a 3+ reaction grade to the patch test when compared to a population whose patch test reactions were obtained from the North American Contact Dermatitis Group (NACDG) database of 1998-2002. This database consisted of 495 individuals. The history of these individuals is not known. It was desired that the dose-response observed in this study be representative of the Cr(VI) sensitized population in the United States. To accomplish this, the following procedure, from page 102 of MRID 46884001, was followed, as reproduced from the report (below):

The extrapolation approach for Scenario 1 for the 90-ng/cm^2 dose is described in detail as an example. In Scenario 1, the 90-ng Cr(VI)/cm^2 dose group had 2 of 60 (3%) participants with allergic response, and both had 3+ grades on their initial patch test. Thus, the participants with allergic responses to the 90-ng Cr(VI)/cm^2 dose, by patch test grade, were 0/33 (0%) 1+, 0/11 (0%) 2+, and 2/16 (13%) 3+. Next, the number of responses to 90 ng/cm^2 was estimated for the NACDG population. Because none of the participants with 1+ or 2+ patch-test grades responded to the 90-ng/cm^2 ROAT challenge, it was assumed that none of the 312 individuals with 1+ grade or the 145 individuals with 2+ patch test grade in the NACDG database would have responded to the 90-ng/cm^2 ROAT challenge (Table 15). Of the ROAT participants with a 3+ patch-test grade, 13% responded to the 90 ng/cm^2 dose. Thus, it was assumed that 13% of the 38 individuals with a 3+ patch-test grade in the NACDG database would have responded to the 90-ng/cm^2 ROAT challenge (13% × 38 = 4.8 individuals). Thus, of the 495 individuals patch tested by the NACDG during 1998–2002, it was assumed that 4.8 (~1%) would have responded at 90 ng/cm^2 in the ROAT. The same procedure was applied for the 250, 750, and 2500 ng Cr(VI)/cm^2 dose groups to obtain their response fractions. The patch-test normalization calculations for Scenarios 1 and 2 are described in Appendix L.

On the basis of the normalized results, benchmark dose modeling was conducted on the dose-response data. Modeling was conducted on both the original data and the normalized data. Results for the calculation of 10% minimum elicitation thresholds were derived and presented on page 108 of the report in summary form.

When considering only allergic reactions, the original calculated 10% MET of 270 ng/cm^2 is approximately 3-fold higher than the 10% MET value derived from the study of Nethercott et al. (88 ng/cm^2). The normalized value of 349 ng/cm^2 is even higher. Reasons that the calculated 10% MET in this study are higher than previously reported by Nethercott et al. include normalization of the test results in this study, use of a wood treatment solution containing Cr(VI) compared to use of potassium dichromate, and use of an open application test compared to use of occluded conditions. Occluded conditions might be expected to result in lower threshold values compared to open application tests. The present ROAT study included experimentation on the same test subjects using potassium dichromate, a form of hexavalent chromium that is typically used for examination of dermal sensitization to hexavalent chromium. Results of that study showed original 10% MET value of 118 ng/cm^2 for non–normalized data involving only allergic responses, and a 10% MET of 86.6 ng/cm^2 when allergic and irritant responses were combined. The patch test normalized values for potassium dichromate were 364 and 269 ng/cm^2 for allergic responses and allergic plus irritant responses, respectively. Of interest is the comparison of the MET values for both the CopperShield® treatment solution and the potassium dichromate solution. The original, non-normalized dose-response data show a difference in the 10% MET values between the wood treatment solution and potassium dichromate. That is, the potassium dichromate 10% MET value is lower (118 ng/cm^2) compared to the wood treatment solution 10% MET (270 ng/cm^2). However, when the dose-response data was normalized on the basis of patch test data from the NACDG database, the 10% MET values are almost the same between the two forms of Cr(VI) tested (349 and 364 ng/cm^2 for the wood treatment solution and potassium dichromate, respectively). A similar result can be seen using the dose-response data that combined allergic and irritant responses.

Classification

This study is classified **acceptable/non-guideline** and fulfills the purpose for which it was conducted. However, determination of a single 10% MET value will require further discussion within the Office of Pesticide Programs.