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

004398

MAR 12 1985

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Omadine MDS (Sodium or Zinc)-18-Month Skin Painting Carcinogenicity Study in CD-1 Mice. EPA Reg. No. 1258-840; 1258-842.

Caswell No. 621D

TO: John Lee, Product Manager #31
Disinfectant Branch
Registration Division (TS-767)

FROM: Carlos A. Rodriguez CAR 4/1/85
Section VI, Toxicology Branch
Hazard Evaluation Division (TS-769)

THRU: Jane E. Harris, Ph.D. JEH 4/1/85
Section Head, Section VI
Toxicology Branch/HED (TS-769)

Applicant: Olin Corporation
275 South Winchester Avenue
P. O. Box 30275
New Haven, Conn. 06511

Action Requested:

Review the above subject study to become part of the files for the subject EPA Reg. No. 1258-840.

Recommendation:

The skin painting oncogenic evaluation of Omadine MDS is adequate and classified Core-Minimum Study. The study will be part of the files for your product.

Conclusion:

Not oncogenic at 20 mg/kg/ (HDT)

Systemic LEL = 20 mg/kg (increased mortality in both sexes, liver hypertrophy in males)

NOEL = 2 mg/kg

Levels tested: 2 and 20 mg/kg on skin of CD-1 mice

OPP:HED:TOX:CR:sb 3/28/85 X71511 #8-D17

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EPA: 68-01-6561
TASK: 92
March 20, 1985

DATA EVALUATION RECORD

OMADINE-MDS

18-Month Skin Painting Oncogenicity Study in Mice

STUDY IDENTIFICATION: Jefferson, N.D., Blair M., Kopplin, J.R., Richter, W.R. 18-Month skin painting carcinogenicity study in mice with Omadine™-MDS. (Unpublished report No. 397-032 prepared by International Research and Development Corporation, Mattawan, MI for Olin Corporation, New Haven, CT; dated June 15, 1984.) MRID Nos. 254132-254138.

APPROVED BY:

I. Cecil Felkner, Ph.D.
Program Manager
Dynamac Corporation

Signature: I. Cecil Felkner

Date: 3-20-85

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1. CHEMICAL: Omadine

2. TEST MATERIAL: The test material was described as Omadine™-MDS. It was not indicated if the test material was the sodium (EPA Registration No. 1258-842) or the zinc (EPA Registration No. 1258-840) salt. MDS, a shampoo formulation containing 35 percent Malprofix TLS-500, 5 percent Superamide L-9, and 60 percent water was the vehicle. Purity of the test compound was not provided. Chemically analyzed batches of the test compound in vehicle and the vehicle were supplied by the sponsor every three months (CBI page 16, Appendix B). Omadine is 1-hydroxy-2 pyridine thione, an antimicrobial agent.

3. STUDY TYPE: 18-month skin painting oncogenicity study in mice.

4. STUDY IDENTIFICATION: Jefferson, N.D., Blair M., Kopplin, J.R., Richter, W.R. 18-Month skin painting carcinogenicity study in mice with Omadine™-MDS. (Unpublished report No. 397-032 prepared by International Research and Development Corporation, Mattawan, MI for Olin Corporation, New Haven, CT; dated June 15, 1984.) MRID Nos. 254132-254138.

5. REVIEWED BY:

William L. McLellan, Ph.D.
Principal Author
Dynamac Corporation

Signature: William L. McLellan
Date: 20 March, 1985

Finis Cavender, Ph.D.
Independent Reviewer
Dynamac Corporation

Signature: Ira Cecil Felkner for
Date: 3-20-85

6. APPROVED BY:

I. Cecil Felkner, Ph.D.
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Signature: Carlos A. Rodriquez
Date: 3-28-85

Jane Harris, Ph.D.
EPA Section Head

Signature: _____
Date: _____

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7. CONCLUSIONS: Under the conditions of this study, Omadine-MDS was not oncogenic when applied topically to male and female CD-1 mice at levels of 2 or 20 mg/kg, 3 days a week for 18 months. There was an increased mortality in both males and females at 20 mg/kg compared to vehicle controls. A compound-related increase in the incidence of hypertrophy of the liver in males receiving 20 mg/kg compared to controls was found. The vehicle control caused chronic dermatitis and necrotic dermatitis. These lesions were increased in number and/or severity by treatment with 20 mg/kg Omadine-MDS. Based on mortality, hypertrophy of the liver and dermatitis, an LEL of 20 mg/kg and a NOEL of 2 mg/kg can be tentatively established.

CORE CLASSIFICATION: Core minimum.

8. RECOMMENDATIONS: Not applicable.

9. BACKGROUND: Not applicable.

10. DISCUSSION OF INDIVIDUAL TESTS OR STUDIES: Not applicable

11. MATERIALS AND METHODS (PROTOCOLS):

The test material was Omadine-1-OH-2-pyridine thione, an antimicrobial agent. The test article in MDS (a shampoo) was administered dermally to the shaved skin of groups of 75 male and 75 female CD-1 mice at dose levels of 2 or 20 mg/kg, 3 days a week, for 18 months. Negative control groups of 75 mice/sex were administered deionized water and vehicle-control groups were administered 3-4 mg/kg MDS. The animals were observed for toxic signs and mortality or moribundity 3 times a day; body weights were recorded weekly for 13 weeks and monthly thereafter. Food consumption was measured for 10 mice/group at the same intervals. Hematology was determined on 10 mice/sex/group at 6, 12, and 18 months. All animals that died, were sacrificed moribund, or sacrificed by design (18 months) were examined grossly. Gross lesions from all animals were examined microscopically. Kidneys, urinary bladder, thyroid, treated and untreated skin from all animals in the negative-control group and low-dose group were examined histologically. A complete set of tissues was examined microscopically for the vehicle-control and high-dose groups.

See Appendix A for detailed protocol (CBI pp 1-3, 12-13, 17, 22-23).

12. REPORTED RESULTS:

Dosing/Analysis: The dosing volume was calculated on the basis of analytically determined concentrations of the test article provided

by the sponsor. Analysis of samples at monthly intervals indicated that the test material was stable for the period of use. Freshly prepared and analyzed batches of vehicle and test compound diluted in vehicle were provided by the sponsor every three months (Appendix B).

Observations and Mortality: Animals in the vehicle-control group showed signs of mild dermal irritation with reddening and some thickening of the skin. Dermal irritation was similar in the group painted with 2 mg/kg but more severe dermal irritation with scabbing and abrasion was evident in the 20 mg/kg groups. Males also experienced irritation in the anogenital region. The incidence of these signs increased with dose, being 6, 7, 8, and 11 of 75 in negative-control, vehicle-control, 2 mg/kg, and 20 mg/kg groups of males, respectively. During the first 20 weeks of the study, a "majority" of mice in the vehicle-control and Omadine-MDS-treated groups exhibited behavioral changes on the days of dosing, e.g., vigorously moving food retainers in the food jars. Midway in the study there was a dose-related increase in the incidence of mice with abnormal positional changes including decrease usage of the hind limbs and an increase in limbs hanging out of the cage.

Mortality and survival at 15 and 18 months are presented in Table 1. Survival at 15 months ranged from 67 to 95 percent. Mortality was increased for the vehicle control, 2 and 20 mg/kg males, and 20 mg/kg females as compared to negative controls. Compared to vehicle controls, mortality was increased in males and females in the 20 mg/kg group at 15 and 18 months.

Body Weights and Food Consumption: The mean body weights of both males and females in the vehicle control and Omadine-MDS groups were increased when compared to negative controls. The mean body weights in vehicle-control groups were similar to those in groups topically administered the test substance (Table 2). Food consumption was frequently increased in the 20 mg/kg group as compared to the vehicle-control groups of males and females. Mean food consumption was lower in the negative-control groups compared to other groups (Table 3).

Hematology: Although there were statistically significant differences between mean values for some hematology parameters, the values were within the normal range of variability and there were no dose- or time-related trends. Therefore, it was concluded that there were no compound related effects on hematology.

Organ Weights: No organ weights were reported.

TABLE 1. Mortality and Percent Survival in Mice for 18-Month Skin Painting with Omadine

Group[a]	Number Dead at Month 15	18
Male		
Negative Control	4 (95)[b]	11 (85)
Vehicle Control	14 (81)	20 (73)
2 mg/kg	16 (79)	26 (65)
20 mg/kg	25 (67)	42 (44)
Female		
Negative Control	7 (91)	13 (83)
Vehicle Control	8 (89)	14 (81)
2 mg/kg	4 (95)	13 (83)
20 mg/kg	9 (88)	25 (67)

[a] 75 animals/group/sex initially.

[b] The number in parenthesis is percent survival.

TABLE 2. Selected Mean Body Weights of Mice Treated with Omadine-MDS for 18 Months

Group[1]	Mean Body Weight (g) at Week 13	26	52	78
		Males		
Negative Control	34 ±1.9[2]	37 ±2.3	38 ±2.8	38 ±2.9
Vehicle Control	35 ±2.4	37 ±2.7	39 ±3.4	39 ±2.8
2 mg/kg	35 ±2.1	37[a] ±2.3	39 ±2.5	38 ±2.2
20 mg/kg	35 ±2.3	37 ±2.1	39 ±2.8	39 ±2.2
		Females		
Negative Control	29 ±1.7	30 ±2.1	33 ±2.8	34 ±2.6
Vehicle Control	31[a] ±1.6	32[a] ±2.0	34[a] ±2.4	36[a] ±4.2
2 mg/kg	31[a] ±2.0	33[a] ±2.4	35[a] ±4.0	35 ±3.1
20 mg/kg	31[a] ±1.8	33[a,b] ±2.0	35[a] ±2.3	35[a] ±2.5

[1] There were 75 mice/group/sex at initiation.

[2] Standard deviation.

[a] Significantly different from negative control at $p < 0.01$.

[b] Significantly different from vehicle control at $p < 0.05$.

TABLE 3. Selected Mean Food Consumption in g/kg/day for Mice Treated with Omadine-MDS for 18 Months

Group[1]	Mean Food Consumption (g) at Week 13	26	52	78
		MALES		
Negative Control	135.8 ±15.50[2]	156.3 ±11.92	142.6 ±13.30	155.3 ± 8.95
Vehicle Control	152.5 ±15.02	164.2 ±27.02	148.5 ±24.69	169.2[a] ±10.30
2 mg/kg	158.4[a] ±28.46	161.6 ±15.43	157.3[a] ±12.55	171.4[a] ± 9.83
20 mg/kg	165.7[b] ±14.67	177.4[a] ±15.99	174.8[b,c] ±10.52	172.2[b] ±16.13
		FEMALES		
Negative Control	174.7 ±26.50	183.9 ±19.63	167.2 ±11.28	172.9 ± 5.62
Vehicle Control	191.6 ±28.42	199.7 ±23.96	175.4 ±15.96	185.8[b] ±12.22
2 mg/kg	182.3 ±13.65	199.0 ±32.47	186.4 ±22.61	189.4 ±39.37
20 mg/kg	190.9 ±23.03	214.2[a] ±31.25	203.9[b,c] ±19.58	202.8[b,c] ± 7.50

[1]Measured for 10 mice/group/sex.

[2]Standard deviation.

[a]Significantly different from the negative control at $p < 0.05$.

[b]Significantly different from the negative control at $p < 0.01$.

[c]Significantly different from the vehicle control at $p < 0.01$.

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Gross Pathology: Skin lesions were seen at the site of application in male and female mice in the vehicle and test groups. These lesions consisted of thickening, scabbing, abrasion, encrustation, erosion, ulceration, subcutaneous edema, and vascularity. The incidence of grossly observed skin lesions is summarized in Table 4. The incidence of all lesions was high in the vehicle-control animals and the incidence and severity of all lesions except thickening appeared to be somewhat higher in males and females at 20 mg/kg than in controls. The authors stated that "skin at sites other than the application site showed a low incidence of lesions such as abrasions, scabs, encrustation, and ulceration" in vehicle and test groups. Incidence of these lesions is summarized in Table 5. An increased incidence of urinary bladder distension occurred in males in the vehicle-control and test groups, the incidence being 3, 18, 20, and 35 of 75 in the negative controls, vehicle controls, the 2 mg/kg, and the 20 mg/kg groups, respectively. There was also an increased incidence of penile lesions (paraphimosis and ulcerated foreskin) in high-dose males that died during the study as compared either to negative or vehicle controls (5 of 42 for high-dose males compared to 0 of 20 for vehicle controls).

Histopathology: Table 6 summarizes the incidence of neoplastic lesions in male and female mice. There was a slight increase in the incidence of hepatocellular adenomas and carcinomas in males administered 20 mg/kg Omadine-MDS but compared to vehicle control the increase was not statistically significant. A compound-related hypertrophy of the liver in males at the 20 mg/kg dose level was also found. Also, an increased incidence in malignant lymphomas in the 20 mg/kg group of females was noted as compared to vehicle controls. The incidence of chronic dermatitis was similar in vehicle control and dosed groups but there was a dose-related increase in necrotic dermatitis in both males and females administered 20 mg/kg Omadine. This lesion was also found in vehicle-control mice but not in negative-control mice (Table 7).

"Other frequently observed microscopic changes included chronic nephritis, colloid cysts in the thyroid, lymphocytic infiltration in the urinary bladder, interstitial pneumonia, alveolar broncheolar adenomá, ovarian cysts, and uterine cystic hyperplasia." It was stated that these changes were not related to dosing and were spontaneous in nature. Table 8 summarizes non-neoplastic lesions other than those in the skin.

TABLE 4. Grossly Observed Lesions in Skin at the Application Site of Mice Administered Omadine-MDS

Skin Lesion	Males[a]				Females[a]			
	Controls[b]		Omadine-MDS (mg/kg)		Controls[b]		Omadine-MDS (mg/kg)	
	NC	VC	2	20	NC	VC	2	20
Thickened (total)	0	67	56	61	1	64	65	58
trace	0	4	5	3	0	9	10	0
mild	0	54	49	38	1	54	52	49
moderate	0	9	2	20	0	1	3	9
Scabbed, crusty, abraded (total)	0	18	9	32	1	19	14	47
trace	0	0	1	1	1	18	11	36
mild	0	18	8	31	0	1	3	11
Edema, subcutaneous, mild; vascularization	0	8	10	20	0	10	13	24

[a]There were 75 mice/group/sex.

[b]NC - negative control; VC - vehicle control.

TABLE 5. Grossly Observed Lesions of Non-application Site Skin in Mice Administered Omadine-MDS

	Males[a]				Females[a]			
	Controls		Omadine-MDS (mg/kg)		Controls		Omadine-MDS (mg/kg)	
	NC	VC	2	20	NC	VC	2	20
Abdomen, thorax, limb-scabbed, abraded, scaley								
mild	0	0	0	7	0	1	3	8
moderate or severe	0	0	0	3	0	0	0	1
Tail-necrotic, edematous, and scabbed	1	0	2	3	0	0	2	2
Hair loss	0	0	2	6	0	1	0	8
Masses	0	0	0	2	2	0	1	5

[a]There were 75 mice/group.

TABLE 6. Incidence of Primary Neoplastic Lesions in Mice Dermally Administered Omadine-MDS[a]

Tissue/Tumor	Males				Females			
	Controls[b]		Omadine-MDS (mg/kg)		Controls[b]		Omadine-MDS (mg/kg)	
	NC	VC	2	20	NC	VC	2	20
Liver	(11)[c]	(75)	(15)	(75)	(2)	(75)	(4)	(75)
hemangioma	2	0	0	0	0	0	0	0
hepatocellular adenoma	3	7	8	12[d]	0	4	2	6
hepatocellular carcinoma	1	2	3	1	0	0	0	1
adenoma or carcinoma	4	9	11	13	0	4	2	7
Lung	(15)[c]	(75)	(10)	(75)	(9)	(74)	(10)	(75)
adenoma	8	12	7	7	5	11	7	9
carcinoma	1	1	1	0	0	0	1	0
Lymphoreticular system	(4)[c]	(75)	(2)	(75)	(4)	(75)	(5)	(75)
lymphoma, lymphocytic	4	3	2	2	0	2	0	3
lymphoma, histocytic	0	0	0	0	4	2	4	3
lymphoma, mixed	0	0	0	0	0	1	1	6[d]
total lymphomas	4	3	2	2	4	5	5	12
Uterus					(51)[c]	(75)	(52)	(75)
hemangioma					0	1	1	0
leiomyoma					0	1	1	3
polyp					3	4	2	1
adenocarcinoma					1	0	0	0
hemangiosacrcoma					1	0	0	0
leiomyosarcoma					1	0	0	0
total tumors					6	6	4	4

[a] Tissues with a sporadic tumor are not tabulated.

[b] NC - Negative control; VC - vehicle control.

[c] Number in parenthesis is number of tissues or animals examined histologically.

[d] Found not to be significantly different from the vehicle control at $p < 0.05$ using the Fisher exact test; analysis by our reviewers.

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TABLE 7. Incidence of Frequently Occurring Non-Neoplastic Lesions (Except Dermal) in Mice Administered Omadine-MDS

	Males				Females			
	Controls[a]		Omadine-MDS (mg/kg)		Controls[a]		Omadine-MDS (mg/kg)	
Tissue/Lesion	NC	VC	2	20	NC	VC	2	20
Adrenal	(0)[b]	(75)	(0)	(75)	(0)	(72)	(0)	(75)
A-cell hyperplasia	0	17	0	11	0	30	0	24
Kidney	(75)[b]	(75)	(75)	(74)	(75)	(75)	(75)	(75)
chronic nephritis	48	54	46	52	48	49	45	37
pyelitis	4	3	3	4	5	5	6	8
Liver	(11)[b]	(75)	(75)	(75)	(2)	(75)	(4)	(75)
hypertrophy	0	1	0	9*	0	1	0	2
necrosis	1	9	1	5	0	4	0	5
Lung	(15)[b]	(75)	(10)	(75)	(9)	(74)	(10)	(75)
interstitial pneumonia, trace to mild	2	8	0	18*	2	13	1	29*
adenomatous hyperplasia	0	12	1	7	0	4	0	1
Lymph Node	(2)[b]	(3)	(4)	(11)	(1)	(5)	(2)	(15)
lymphoadenitis	0	0	0	3	0	0	0	0
hyperplasia, reticuloendothelial	0	0	0	5	0	0	1	2
Prostate	(3)[b]	(75)	(15)	(74)				
acute prostatitis	0	0	0	7*				
Salivary gland	(0)[b]	75	(0)	(74)	(0)	(75)	(0)	(74)
sialoadenitis	0	3	0	7	0	8	0	5
Spleen	(6)[b]	(75)	(4)	(75)	(21)	(74)	(6)	(75)
increase extramedullary hemopoiesis	1	0	1	5	1	6	3	12
Testis	(2)[b]	(75)	(0)	(75)				
testicular degeneration	2	13	0	4				
Thyroid	(75)[b]	(74)	(74)	(63)	(75)	(69)	(75)	(73)
colloid cyst	19	31	24	26	28	22	24	30
Bladder	(75)[b]	(75)	(75)	(75)	(74)	(75)	(75)	(75)
hyperplasia	0	0	0	2	0	0	0	0
cystitis	2	3	5	5	0	2	1	2
lymphoid infiltration	12	11	17	14	20	21	24	17

TABLE 7. Incidence of Frequently Occurring Non-Neoplastic Lesions (Except Dermal) in Mice Administered Omadine-MDS (continued)

Tissue/Lesion	Males				Females			
	Controls[a]		Omadine-MDS (mg/kg)		Controls[a]		Omadine-MDS (mg/kg)	
	MC	VC	2	20	MC	VC	2	20
Ovary					(29)[b]	(74)	(28)	(74)
cyst					27	36	25	36
Uterus					(54)[b]	(75)	(52)	(75)
cystic hyperplasia					46	56	46	22
Stomach	(5)[b]	(75)	(5)	(75)	(8)	(75)	(14)	(75)
hyperplasia	3	2	0	1	7	5	12	6

[a] NC - negative control; VC - vehicle control.

[b] Number of tissues examined histologically.

* Statistically different from vehicle control ($p < 0.05$) using the Fisher exact test; analysis by our reviewers.

TABLE 8. Incidence and Severity of Histologic Lesions of the Skin in Mice Administered Omadine-MDS Dermally

Skin/Lesion	Males				Females			
	Controls[a]		Omadine-MDS (mg/kg)		Controls[a]		Omadine-MDS (mg/kg)	
	NC	VC	2	20	NC	VC	2	20
Application Site	(75)[b]	(75)	(75)	(75)	(75)	(75)	(74)	(75)
Dermatitis (total)	0	60	66	50	1	67	69	62
trace	0	17	35	5	0	26	31	2
mild	0	42	40	24	1	39	36	25
moderate	0	1	1	21	0	2	2	35
Ulceration								
mild	0	0	0	1	0	0	0	0
moderate	0	0	0	1	0	0	0	0
Necrotic dermatitis (total)	0	12	6	22	0	8	3	13
mild	0	12	5	7	0	8	2	5
moderate	0	0	1	15	0	0	1	8
Non-application site	(75)[b]	(75)	(75)	(74)	(75)	(75)	(74)	(74)
Dermatitis	2	0	4	11	0	2	1	9
trace	0	0	3	8	0	1	1	4
mild	2	0	1	3	0	0	0	4
moderate	0	0	0	0	0	1	0	1
Ulceration, moderate	0	0	0	1	0	0	0	0
Necrotic dermatitis (total)	0	0	2	11	0	0	0	6
mild	0	0	2	8	0	0	0	2
moderate	0	0	0	3	0	0	0	4

[a] NC - negative control; VC - vehicle control.
[b] Number of tissue examined histologically.

13. STUDY AUTHOR'S CONCLUSIONS/QUALITY ASSURANCE MEASURES:

Under the conditions of the study, Omadine was not oncogenic in mice when administered to the shaved skin at levels of 20 mg/kg, 3 days a week for 18 months. The increase in hepatocellular tumors (adenomas and carcinomas) in males was not considered "toxicologically significant" when compared to vehicle control. The comparison to negative controls was stated not to be valid since only 11 livers were examined.

The authors presented their laboratory's historical data for malignant lymphoma in the strain of mice used in the present study. In six 18-month studies, the incidence in 340 males was 4.1 percent (range 1.7 to 10 percent) and the incidence in 300 females was 7.0 percent (range 2.0 to 13.3 percent). The incidence for malignant lymphomas in females receiving 20 mg/kg in the present study was 16 percent which was stated "within the historical control range for this laboratory."

Application of Omadine-MDS "resulted in thickened skin, certain behavioral changes, and distended urinary bladders (in males) with signs of irritation in the anogenital area." All these findings occurred in the vehicle-control groups as well. The response in the 2 mg/kg group was identical to the vehicle-control group. There was a higher degree of skin irritation and a significant increase in mortality in the 20 mg/kg groups of males and females compared to vehicle controls. Other findings were considered comparable between vehicle-control and dosed groups.

A quality control report signed and dated June 24, 1983 was present.

14. REVIEWERS' DISCUSSION AND INTERPRETATION OF STUDY RESULTS:

Our reviewers agree with the study authors' conclusion that under the conditions of the study Omadine-MDS was not oncogenic. The reasons for our conclusion, however, differ from those of the study authors. When we statistically analyzed the incidence of any type of lymphoma or combined lymphomas using the Fisher exact test or chi-square, there were no significant differences at a p value of 0.05 when the high- or low-dose group were compared to the vehicle control or negative controls. The authors noted an increase in incidence of lymphomas in females at 20 mg/kg and stated that the increase was of doubtful toxicologic significance since the incidence in high-dose females (16 percent) was within the range for historical controls. The proper comparison to make would have been the concurrent vehicle control and the historical control. The historical laboratory incidence for six 18-month studies was 7.0 percent (range 2.0-13.3 percent) which is similar to the concurrent vehicle control incidence (5/75 or 7 percent).

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When the incidence of liver adenomas or total hepatocellular tumors was analyzed statistically, we found no significant increase over vehicle controls. Appropriate statistical analysis was not provided by the study authors. The incidence of tumors was not analyzed, rather, survival data and time to tumor death were analyzed for each individual type of tumor. There was a significance in the time to adenoma when vehicle control and males receiving 20 mg/kg were compared.

A valid comparison of the incidence of hepatocellular tumors in negative controls and Omadine-MDS treated mice could not be made because livers were histologically examined in only 11 negative control males and 2 negative control females.

In general, there are several deficiencies in the study design which limit the study's sensitivity to assess oncogenicity. There were only two dose levels rather than three for the test materials and no organ weights were taken for mice at terminal sacrifice. The test site was not covered with a dressing, nor was it washed before application of test material. This may have allowed the vehicle or test compound to accumulate on the application site. In addition, the choice of vehicle was not prudent because it caused toxicity and irritation.

There was an increase in the severity of dermatitis and chronic dermatitis in both males and females administered Omadine-MDS topically at a level of 20 mg/kg. No apparent increase compared to vehicle control was noted at 2 mg/kg. It is difficult to judge the severity of the dermatitis because it was of high incidence in animals administered the vehicle. There was an increased incidence of dermatitis at the non-application sites at 20 mg/kg but no effect of the vehicle control.

15. CBI APPENDIX:

A - Materials and Methods (Protocols), CBI pp. 1-3, 12-13, 17, 22-23.
B - Results (Dosing/Analysis), CBI pp. 16, p. 1 of Appendix A "Sponsor-Generated Analytical Results."

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APPENDIX A

Materials and Methods (Protocols)

Document Received

Page _____ is not included in this copy.

Pages 19 through 29 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 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.

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