CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20-969

PHARMACOLOGY REVIEW(S)

Division of Oncology Drug Products, HFD-150
Review and Evaluation of Pharmacology and Toxicology Data
Review No. 2, Filename uvalabel.doc

IND 20-969	Serial # 000	Type: NDA
	Received by CDR	February 25, 1998
	Letter Dated	February 20, 1998
	Review Completed	February 20, 1999

Key Words: Labeling, photopheresis, cutaneous T-cell lymphoma and methoxsalen

Title: 8-Methyoxypsoralen for use with the UVAR photopheresis system in the palliative treatment of the skin manifestations of Cutaneous T-Cell Lymphoma.

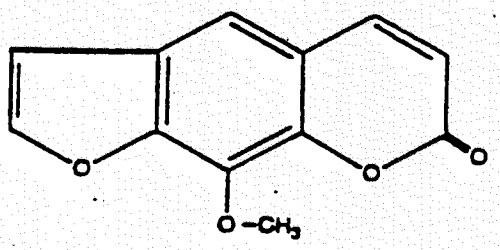
Reviewer: W. David McGuinn, Jr., Ph. D., D.A.B.T.

Sponsor: Therakos, Inc.
Extron, PA

Information to be conveyed to the sponsor: **YES**

Drug Name: UVADEX,
Generic Name: methoxsalen, 8-MOP
Chemical Name: (9-methoxy-7H-furo[3,2-g][1]-benzopyran-7-one)
CAS Registry: 298-81-7

Structure:



Molecular Formula: $C_{12}H_8O_4$
FW: 216.18

Essential Device: Therakos UVAR Photopheresis System
Related INDs & NDAs: IND
IND
IND
IND
IND
IND
IND
NDA 20-969

Class: Extracorporeal Photopheresis

Indications: Palliative treatment of the skin manifestations of Cutaneous T-Cell Lymphoma

Dose: 200 µg per dose, 270 ng/ml in the white cell treatment bag.
This is about 118 µg/m^2 if we assume that the entire dose is infused back into the body. But, much of the compound is photolyzed before reinfusion so the actual dose is much lower.

Frequency: Twice a week

Route: extracorporeal treatment of centrifugally separated white cells.

Previous Reviews:

1) W. David McGuinn, Jr., Ph. D. Reviewed NDA 20-969 (review #1) February 19, 1999.

Studies Reviewed within this submission:

None

I have excerpted portions of this review from the sponsor's submission.

Labeling Changes:

Replace the text of the Carcinogenicity, Mutagenesis, and Impairment of Fertility section with the following and move to the WARNINGS section:

[Note to the sponsor: Please update the following paragraph using the results from Stern *et al.* 1998, *Journal of the National Cancer Institute*, 90(17):1278-1284]

Redacted 1

pages of trade

secret and/or

confidential

commercial

information

Recommendation:

The pharmacological or toxicological information provided in this submission is sufficient to establish that this therapy can be approved for palliative treatment of the skin manifestations of Cutaneous T-Cell Lymphoma.

/S/

W. David McGuinn, Jr., Ph. D., D.A.B.T.
February 20, 1999
Modified February 24, 1999

cc: IND 40,482
NDA 20-969
HFD-150 Division File
/W D McGuinn
/P Andrews
/S Hirschfeld
/D Catterson

/S/
2/24/99

February 24, 99

NDA 20-969

Division of Oncology Drug Products, HFD-150
Review and Evaluation of Pharmacology and Toxicology Data
Review No. 1, Filename 20969_01.doc

IND 20-969	Serial # 000	Type: NDA
	Received by CDR	February 25, 1998
	Letter Dated	February 20, 1998
	Review Completed	February 19, 1999

Keywords: 8-Methyoxypsoralen, carcinogenicity, photopheresis, cutaneous T-cell lymphoma.

Title: 8-Methyoxypsoralen for use with the UVAR photopheresis system in the palliative treatment of the skin manifestations of Cutaneous T-Cell Lymphoma.

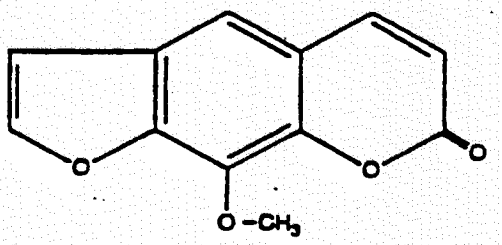
Reviewer: W. David McGuinn, Jr., Ph. D., D.A.B.T.

Sponsor: Therakos, Inc.
Extron, PA

Information to be conveyed to the sponsor: **NO**

Drug Name: UVADEX,
Generic Name: methoxsalen, 8-MOP
Chemical Name: (9-methoxy-7H-furo[3,2-g][1]-benzopyran-7-one)
CAS Registry: 298-81-7

Structure:



Molecular Formula: $C_{12}H_8O_4$
FW: 216.18

Essential Device: Therakos UVAR Photopheresis System
Related INDs & NDAs: IND
IND
IND
IND
IND
IND
IND
NDA 20-969

NDA 20-969

NDA 9-049

Class: Extracorporeal Photopheresis
Indications: Palliative treatment of the skin manifestations of Cutaneous T-Cell Lymphoma

Dose: 200 μg per dose, 270 ng/ml in the white cell treatment bag.
This is about 118 $\mu g/m^2$ if we assume that the entire dose is infused back into the body. But, much of the compound is photolyzed before reinfusion so the actual dose is much lower.
Frequency: Twice a week

Route: extracorporeal treatment of centrifugally separated white cells.

Previous Reviews:

1) Dr. A. W. Coulter reviewed the initial submission to HFD-150 on October 19, 1992. This review contains no new pharmacology or toxicology data; the IND referred to NDA9-049.

NDA 20-969

Studies Reviewed within this submission:

PREVIOUS REVIEWS: 2
STUDIES REVIEWED WITHIN THIS SUBMISSION: 3
STUDIES SUBMITTED BUT NOT REVIEWED: 5
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2) D C Mays et al., 1985. Disposition of 8-methoxypsoralen in the rat: methodology for measurement, dose-dependent pharmacokinetics, tissue distribution and identification of metabolites. J. Pharmacol. Exp. Ther. 236(2):364-373. Volume 10, page 290. 8
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2) A Apostolou et al. 1979. Acute Toxicity of Micronized 8-Methoxypsoralen in Rodents. Drug and Chemical Toxicology, 2(3): 309-313. 12
3) A. Langner et al (1977). Dermal Toxicity of 8-methoxypsoralen administered (by gavage) to hairless mice irradiated with long wavelength ultraviolet light. Journal of Investigative Dermatology, 69:451-457. 13
4) NTP Technical Report on the Toxicology and Carcinogenesis Studies of 8-Methoxypsoralen in F344/N Rats (gavage studies). NIH Publication number 89-2814. Sixteen Day Study. Volume 8, page 58. 14
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1) H. A. Navarro et al, 1991. National Toxicology Program, Study Number TER-91-017. Developmental toxicity evaluation of 8-methoxypsoralen administered by gavage to Sprague-Dawley rats on gestational days 6 through 15. Volume 10, page 13. 24
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1) R. S. Stern et al. 1979. Risk of cutaneous carcinoma in patients treated with oral methoxsalen photochemical-therapy for psoriasis. New England Journal of Medicine 300(15):811-813. Volume 10, page 276. 29
2) NTP Technical Report on the Toxicology and Carcinogenesis Studies of 8-Methoxypsoralen in F344/N Rats (gavage studies). NIH Publication number 89-2814. Two-year carcinogenicity study. Volume 8, page 58. .. 29
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1) NTP Technical Report on the Toxicology and Carcinogenesis Studies of 8-Methoxypsoralen in F344/N Rats (gavage studies). NIH Publication number 89-2814. Ames Test. Volume 8, page 58. 36
2) NTP Technical Report on the Toxicology and Carcinogenesis Studies of 8-Methoxypsoralen in F344/N Rats (gavage studies). NIH Publication number 89-2814. Chinese Hamster Ovary Cytogenetics Assay. Volume 8, page 58. 38

3) P Weniger. 1981. A comparison of the photochemical actions of 5 and 8-methoxypsoralen on CHO cells. Toxicology 22:53-58. Volume 10, page 258. ..... *40*

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OVERALL SUMMARY: **42**

RECOMMENDATION: **45**

LABELING COMMENTS: 45

Studies Submitted but Not Reviewed:

1) M K Polano and A A Schothorst, 1977. Differences in efficiency of two delivery forms of 8-methoxy psoralen. *Dermatologica* **154**:216-218. Volume 8, page 1.
2) D H Palmer and R Rusignuolo, 1990, Acute Intravenous toxicity testing in mice with Ro 21-4245/000 injectable (Study No 05619). Hoffmann-La Roach internal report. Volume 8, page 4.
3) J K Dunnick *et al.*, 1987. Toxicity of 8-methoxypsoralen, 5-methoxypsoralen, 3-carbethoxypsoralen or 5-methylisopsoralen with ultraviolet radiation in the hairless (HRA/Skh) mouse. *Toxicology and Applied Pharmacology*, **89**:73-80. Volume 8, page 31.
4) J K Dunnick *et al.*, 1984. Subchronic toxicity in rats administered oral 8-methoxypsoralen. *National Cancer Institute Monograph* **66**:91-95. Redundant see NCI monograph reviewed below. Volume 8, page 39.
5) J K Dunnick and M R Elwell, 1988. Toxicity studies of amphetamine sulfate, ampicillin trihydrate, codeine, 8-methoxypsoralen, α-methyldopa, penicillin VK and propantheline bromide in rats and mice. *Toxicology*, **56**:123-136. Volume 8, page 44.
6) L. K. Roberts et al. 1979. Tumor susceptibility generated in mice treated with subcarcinogenic doses of 8-methoxypsoralen and long wave ultraviolet light. *Journal of Investigative Dermatology*, **72**:306-309, Volume 10 page 205.
7) A. Chetelat *et al.*, 1993. Photomutagenesis tests development: I. 8-methoxypsoralen , chlorpromazine and sunscreen compounds in bacterial yeast assays. *Mutation Research*, **292**:241-250. Volume 10, page 209.
8) C. Bauluz *et al.* 1991. Further studies on the lethal and mutagenic effects of 8-methoxypsoralen-induced lesions on plasmid DNA. *Cellular and Molecular Biology*, **37**(5):481-500. Volume 10, page 219.
9) E J Gunther *et al.*, 1995. Mutagenesis by 8-methoxypsoralenand 5-methylangelicin photoadducts in mouse fibrobasts: mutations at cross-linkable sites induced by monoadducts as well as cross-links. *Cancer Research* **55**:1283-1288. Volume 10, page 246.
10) D. Papadopoulo et al. 1983. Mutagenic effects of 3-carbethoxypsoralen and 8-methoxypsoralen plus 365 nm irradiation in mammalian cells. Mutation Research 124:283-297. Volume 10, page 247.
11) A. Chetelat *et al.*, 1993. Photomutagenesis tests development: II. 8-methoxypsoralen , chlorpromazine and sunscreen compounds in bacterial yeast assays. *Mutation Research*, **292**:251-258. Volume 10, page 264.
12) T Negishi *et al.*, 1992. The genotoxicity of UVA irradiation in Drosophila melanogaster and the synergistic action of 8-methoxypsoralen and UVA. *Carcinogenesis* **13**(8):1433-1436.
13) R S Stern *et al.* 1980. Skin carcinomas in patients with psoriasis treated with topical tar and artificial ultraviolet radiation. The Lancet, April 5, 732-735. Volume 10, page 281.
14) W Wamer *et al.*, 1987. Kinetics of 8-methoxypsoralen and 5-methoxypsoralen distribution in guinea pig serum, epidermis and ocular lens. *Photodermatology*, **4**:236-239. Volume 10, page 300.
15) G. I. Malinin *et al.*, 1982. Kinetics of ^{14}C(5)-8methoxypsoralen distribution in rabbits. *Arch Dermatol. Res.* **273**:319-326. Volume 10, page 304.
16) J G Monbaliu *et al.*, 1988. Pharmacokinetics of 8-methoxypsoralen in the dog. *Biopharmaceutics and Drug Disposition*, **9**:9-17. Volume 10, page 312.
17) M Van Boven *et al.*, 1985. A pharmacokinetic comparison in dogs of eleven brands of 8-MOP and five new formulations. *Photodermatology*, **2**:27-31. Volume 10, page 321.

Introduction and Drug History:

8-MOP is a naturally occurring compound; it is found in low concentrations in a number of vegetables. The compound is a furocoumarin (psoralen) that has a strong UVA absorption. The absorption of a photon causes the formation of a radical. This radical is responsible for most of the pharmacological properties of 8-MOP.

The Food and Drug Administration has approved 8-MOP for the treatment of psoriasis and vitiligo. In this therapy, an adult patient takes 20 to 70 mg of 8-MOP (depending on body weight) orally as capsules. Two hours later, the area of the patient's skin affected by the condition is irradiated with UVA light. The irradiation time depends on the patients skin color, skin type and the number of previous exposures. Patients can be treated every other day for weeks.

The Food and Drug Administration also has approved UVADEX therapy with the UVAR photopheresis system for treatment of Cutaneous T-cell lymphoma (CTCL). In this therapy, patients take oral 8-MOP. The UVAR system then removes a portion of the patient's blood, separates the white cells by centrifugation and exposes these 8-MOP treated white cells to UV light. The system then returns the treated blood to the patient. Initially, Therakos designed this therapy to kill the excess cells of the malignant T-cell clone. Nevertheless, though extracorporeal phototherapy exposes less than 10% of the total body burden of malignant cells to 8-MOP plus light, some patients achieve a complete response. This result suggests that the phototherapy activates an immune mediated response against the malignant T-cell clone. To test this hypothesis, Edelson *et al.* (*Photochem-Photobiol.* 1993 Dec., 58(6): 822-6) injected mice with 8-MOP plus UVA treated T-cell lymphoma. This treatment immunized these mice against a subsequent challenge with untreated lymphoma cells. Photopheresis may enhance the immunologic response to class-I tumor associated antigens.

In the therapy of this NDA, the liquid formulation of 8-MOP, UVADEX, is administered to blood fractions *ex vivo*. The liquid 8-MOP is injected directly into a fraction of white cells separated by the original photopheresis device. This is the only difference between the approved photophoresis therapy and the therapy of this NDA; the 8-MOP is injected into the white cell fraction, not taken orally. Therakos has submitted the results of a phase III trial of this therapy in support of NDA 20-969. This trial uses the original UVAR Photopheresis system to treat CTCL.

The Centrinet photopheresis system is an improved version of the original UVAR system. Therakos has tested this system under IDE G910026. These tests used oral 8-MOP and randomized patients into two groups, a control using the old UVAR system (n=9) and a test group using Centrinet (n=6, 24 treatment cycles). In a second single-blind study, five patients with CTCL were treated. *In vitro* data suggests that the UVAR and Centrinet systems cause similar damage to lymphocytes. 8-MOP causes DNA adduct formation when administered 0.3 min before lymphocyte irradiation. This indicates rapid cellular absorption of the drug. I describe the Centrinet system here to avoid confusion in the reviews of this NDA. Therakos has used both systems in their preclinical development of photopheresis therapy. I consider the two systems very similar toxicologically.

The Centrinet system with UVADEX or the UVAR system exposes the patients blood *ex vivo* to at least 270 ng/ml of 8-MOP before irradiation. Thus, 1500-ml blood are treated in a single treatment and the single dose will be at least 75 μg. This is less than $1/500^{th}$ the dose needed when 8-MOP is given orally (~ 40 mg). Thus, even if all the 8-MOP is returned to the patient's systemic circulation the exposure is significantly less than the exposure to 8-MOP by the approved oral route.

I have excerpted portions of this review from the sponsor's submission.

Review

Pharmacokinetics and Toxicokinetics:

1) H. C. Wulf, 1984. Distribution and accumulation of radioactivity in mice following administration of ^{14}C-8-MOP and ^{3}H-8-MOP: an autoradiographic study. *Photodermatology*, **1**:293-297.

Animal	hairless, pigmented Hr/Hr mice
Drug	^{14}C-8-MOP, 115 μCi/mg
	^{3}H-8-MOP, 1560 μCi/mg
Vehicle	Cremophor EL, 20% in water
Dose	^{14}C-8-MOP – 1 mg/kg single dose
	0.7 mg/kg 3 times per week for three weeks (last dose 1 mg/kg)
	^{3}H-8-MOP – 1 mg/kg
Analysis	Microtome sections on film, semi-quantitative measurements by densitometer

The following table shows the time course of ^{14}C-8-MOP distribution after a single doses. The concentrations are arbitrary relative amounts.

	Time after dosing				
	1 hr	3 hr	6 hr	24 hr	168 hr
Blood	2	1.2	1	<0.1	
Lung	2	1			
Connective Tissue	0.6	0.6			
Skin	0.6	0.3			
Muscle		0.3			
Stomach	20	20	7	2.5	5
Small intestine	600	30	55	5	
Colon	0	1250	1350	5	2
Liver	40	20	11	5	0.1
Gall Bladder	500	500	350	11	2.5
Kidney	8	5	1.7	<0.1	0
Urinary Bladder	300	-	1000	5	3

The table suggests that radioactivity is eliminated rapidly in both the urine and feces. Little drug accumulates in the liver. 8-MOP does not appreciably partition into skin, muscle or connective tissue.

The following table compares the distribution of ^{14}C-8-MOP three hours after a single dose to that after the last of nine doses. 8-MOP appears to be eliminated more quickly after multiple doses. This is probably due to induction in the liver. The higher concentrations of radioactivity in the liver and gall bladder are consistent with this hypothesis.

Tissue	Single Dose	Multiple dose
Blood	1	2.3
Lung	0.8	2.6
Connective Tissue	0.5	1.1
Skin	0.2	1.1
Muscle	0.2	0.5
Stomach	16	40
Small intestine	25	120
Colon	1000	1300
Liver	16	50
Gall Bladder	400	540
Kidney	4	8
Urinary Bladder	-	400

^{3}H-8-MOP distribution was similar in all organs but the eye. Here appreciable concentration of radioactivity accumulated in the retina. The author suggests that this is because the tritiated compound is uniformly labeled whereas the ^{14}C compound is labeled at but one position (the 4 Position). He postulated that the radioactivity in the retina is a metabolite that does not contain the ^{14}C label.

2) D C Mays *et al.*, 1985. Disposition of 8-methoxypsoralen in the rat: methodology for measurement, dose-dependent pharmacokinetics, tissue distribution and identification of metabolites. *J. Pharmacol. Exp. Ther.* **236**(2):364-373. Volume 10, page 290.

Animal	Male Sprague-Dawley rats
Body Wt	320 to 360 g
Drug	8-MOP, ^{14}C labeled in the 4 position Or provided by Hoffmann-LaRoche Inc.
Doses	0.2, 1, 2.5, 5, 10, 20 mg/kg, four rats per dose group for PK
Vehicle	30% Emulphor-620 (polyoxyethylated vegetable oil)
Dose Vol.	2 ml/kg
Route	IV, jugular

Analytical Methods – hexane or acetone extraction with HPLC

This was not a GLP study.

The following table shows the major results of the pharmacokinetic analysis. The values are calculated for 8-MOP extracted from plasma. MRT is mean residence time. This parameter is calculated as the maximum of the first moment curve and represents the mean time a molecule is in the body of the rat.

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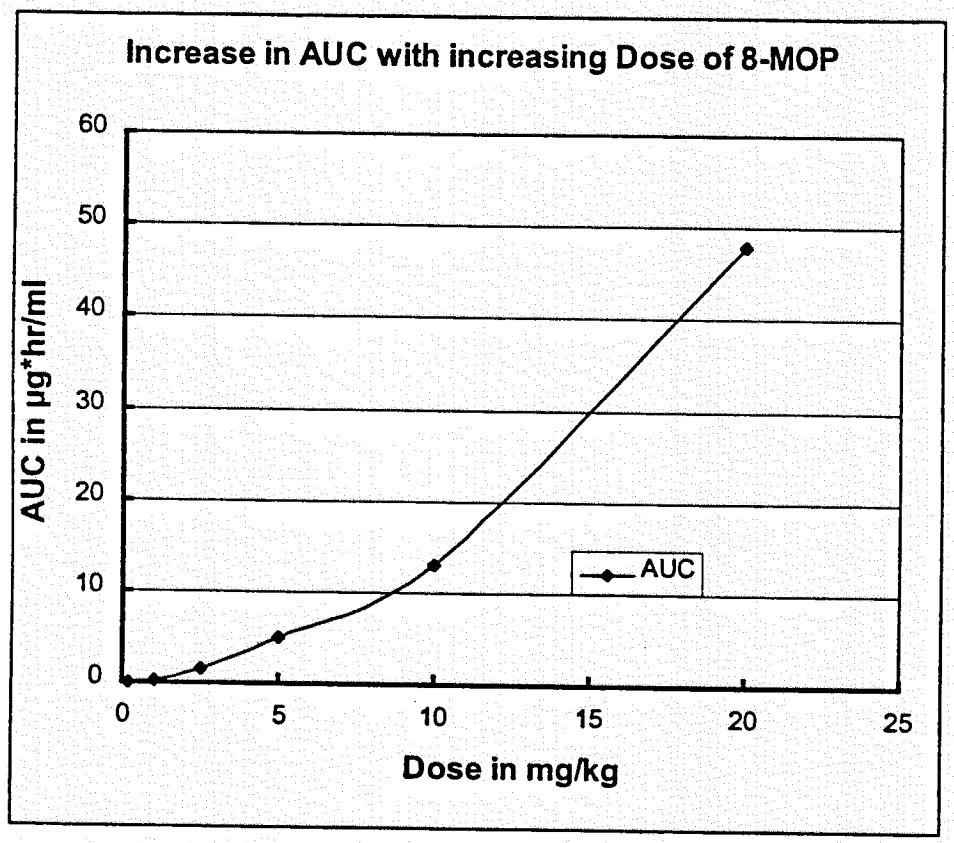
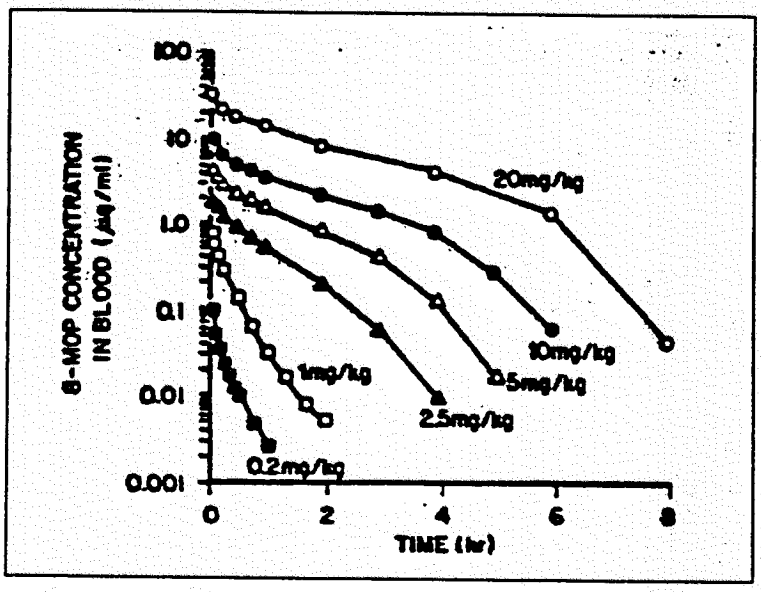
Dose	AUC		Cl		MRT	
mg/kg	µg*hr/ml	sd	L/kg/hr	sd	hr	sd
0.2	0.028	0.003	7.3	0.8		
1	0.27	0.06	3.9	1	0.33	0.05
2.5	1.6	0.3	1.7	0.2	1.13	0.24
5	4.9	0.4	1	0.1	1.57	0.1
10	13	2	0.78	0.14	2.43	0.52
20	47.8	2.6	0.42	0.02	2.9	0.3

The chart below plots AUC with increasing dose. The curve has an inflection point just above 5 mg/kg. This is consistent with a saturable elimination process. Clearance decreases with increasing dose, also suggesting saturable elimination.

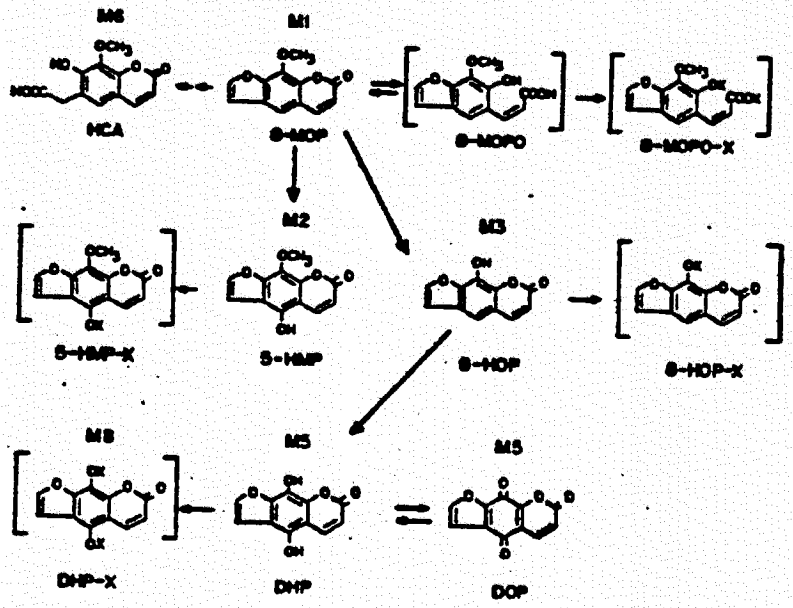


The kinetic curves show an inflection point at an 8-MOP concentration of approximately 1 µg/ml in blood. This is yet further indication of saturable elimination. In the absence of saturation, i.e. at a dose of 0.2 mg/kg, the first order elimination half-life is 0.24 hours.



The graph shows the concentration of 8-MOP in blood after IV dosing with 2 to 20 mg/kg. Rats were given a single IV 30 second injection of ^{14}C-8-MOP via an indwelling jugular catheter. Each point represents the geometric mean of the three or four rats in each dose group. Error bars (not shown) were typically less than 10% of the mean.

From the tissue distribution studies, the authors estimated the volume of distribution to be about 0.8 liters per kilogram. This value is independent of dose and blood concentration. Thus, 8-MOP is widely distributed. The tissue distribution in rats is somewhat different from that in mice (above). The drug concentrations are uniform in most major organs. These concentrations are roughly equal to or slightly less than the concentration in blood. Concentrations four-fold greater than that of blood were found in kidney, three-fold greater in fat, at 0.5 hours. Again, this is somewhat different from the results in mice where more compound was found in the GI. This is attributable to the difference in route. The concentrations in kidney and fat remain high at two hours then diminish sharply at five hours. At five hours, 8.4% of the dose remained in the carcass and the authors had accounted for 98% of the total radioactivity. About 71% of the total radioactivity was eliminated in the urine, about 25% is excreted in the feces. The authors state that dogs given doses of 5 mg/kg IV excrete about 45% in the urine and 40% in the feces. The high concentration of total radioactivity but relatively low concentration of 8-MOP in the liver at 0.5 hours attests to the rapid metabolism of the drug in this organ. The authors detected 11 different metabolites in blood and urine. They identified six of these as 8-hydroxypsoralen, 5-hydroxy-8-methoxypsoralen, 5,8-dihydroxypsoralen, 5,8-dioxopsoralen, 6-(7-hydroxy-8-methoxycoumaryl)-acetic acid. Thus rats metabolize 8-MOP by O-demethylation, hydroxylation at the 5-position, hydrolysis of the lactone ring and oxidation of the furan ring. These pathways are similar to those identified in dogs and humans. The scheme below summarizes the authors proposed pathway for the metabolism of 8-MOP in the rat. Presumptive intermediates and tentatively identified metabolites are shown in brackets. Potential sights for conjugation are marked with an X.



Proposed metabolism of 8-MOP

Pharmacokinetic Summary:

After IV administration to rats, 8-MOP is rapidly and widely distributed. The volume of distribution is about 0.8 liters per kilogram. This value is independent of dose and blood concentration. The first order elimination half-life of small doses is about 0.24 hours. This value increases with dose as does the dose-normalized AUC. Clearance decreases with dose. This is because the elimination mechanisms, probably hepatic, for 8-MOP are saturable. In rats, saturation occurs above a serum concentration of 1μg/ml or 5 μM, a relatively low concentration. The drug concentrations are relatively uniform in most major organs and usually just less than blood concentration. Higher concentrations are found in the liver, kidney and fat in rats. Similar results are seen in dog and humans. In monkeys, the increase in AUC with dose is also nonlinear.

Formulation or particle size in a suspension of oral doses can dramatically affect GI absorption and the resulting toxicological or pharmacokinetic parameters. Pharmacokinetic parameters measured after oral doses are highly variable.

Rats eliminate about 71% of the total radioactivity in the urine, about 25% in the feces. Dogs eliminate about 45% in the urine and 40% in the feces. Most 8-MOP metabolism appears to occur in the liver. Eleven different metabolites have been detected in blood and urine of rats. These include 8-hydroxypsoralen, 5-hydroxy-8-methoxypsoralen, 5,8-dihydroxypsoralen, 5,8-dioxopsoralen, 6-(7-hydroxy-8-methoxycoumaryl)-acetic acid. Thus, rats metabolize 8-MOP by O-demethylation, hydroxylation at the 5-position, hydrolysis of the lactone ring and oxidation of the furan ring. These pathways are similar to those identified in dogs and humans.

NDA 20-969

Toxicology:

1) NTP Technical Report on the Toxicology and Carcinogenesis Studies of 8-Methoxypsoralen in F344/N Rats (gavage studies). NIH Publication number 89-2814. *Single-Dose Study* Volume 8, page 58.

Animal	male and female F344/N rats, five per sex per dose group.
Drug	8-MOP
Lot	21335
Doses	0, 63, 125, 250, 500, or 1000 mg/kg (0, 378, 750, 1500, 3000, 6000 mg/m^2)
Formulation	Corn oil
Route	PO Gavage
Observations	
Clinical signs	Daily for two weeks
No Necropsy	

This was a GLP Study done by SRI Laboratories.

Four of five males and all five females in the 1000 mg/kg dose group died by day 2. No compound related signs were observed in the other dose groups.

2) A Apostolou *et al.* 1979. Acute Toxicity of Micronized 8-Methoxypsoralen in Rodents. *Drug and Chemical Toxicology*, **2**(3): 309-313.

Animals	Holtzman Sprague-Dawley Rats
	CD-1 Mice
	Swiss Webster Mice
Drug	Methoxysalen, Memphis Chemical Co. Cairo Egypt.
Vehicle	10% aqueous gum acacia
Observation	
Mortality	14 day

Species	Strain	Sex	Body Weight	Number of animals	Route	LD50	95% confidence	Calculation Method
						mg/kg		
Rat	Holtzman SD	M	210-310	120	PO	791	590-1059	Weil
Mouse	CD-1	M	24-34	100	PO	699	548-892	Weil
		F	20-32	100	PO	556	466-644	Weil
Mouse	Swiss Webster	M	14-16	50	PO	449	377-534	Finney
		F	14-16	50	PO	423	309-520	Finney
Rat	Holtzman SD	M	160-250	50	IP	189	161-222	Weil
		F	150-210	50	IP	158	128-194	Weil
Mouse	CD-1	M+F	24-40	50	IP	~250		