Rodents dosed with toxic amounts of 8-MOP showed signs of hypoactivity and ataxia. At higher dose levels the animals suffered prostration, muscle twitches and convulsions. Most deaths occurred in the first few days after dosing.

Other sources have reported that the oral LD_{50} of 8-MOP is between 2 and 4 g/kg in rats and mice (see paper for references) and 470 mg/kg IP in rats (Merck Index). The values determined by Apostolou *et al.* are considerably lower than these published results. Indeed their values are considerably lower than those that caused lethality in the NTP study reviewed above. The authors anticipated this difference in the design if their experiments. They meticulously ground dry drug in a mortar and pestle and then continued grinding after the addition of the vehicle. 8-MOP is only poorly soluble in water. Usually dosing preparations are suspensions, not solutions. These studies suggest that the GI absorption of 8-MOP is dependent on particle size in the dosing preparation. This would explain the great variability in plasma concentration of 8-MOP after an oral dose. This pharmacokinetic variability is the very reason that Therakos developed extracorporeal injection of the drug for photopheresis.

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.

Animal	male and female athymic, hairless mice
Weight	about 20 g
Drug	8-MOP
Vehicle	propylene glycol suspension
Concentration	0.01 to 0.5% w/v
Dose volume	0.2 ml
Route	PO, gavage
Schedule	2 to 6 times a week for 1 to 12 months
Irradiation	2 hours after drug administration, 1500 W mercury lamp with glass filter source 30 cm from skin, flux 3300 to 3500 $\mu W/cm^2$, UV dose 0.9 to 1.0 Joules/cm^2 for five minutes irradiation
Observations	
Clinical Signs	daily, skin lesions
Other	DNA synthesis in epidermal cells evaluation of cellular immunity Immunofluorescence in skin, serum directed against UV denatured DNA
Histopathology	Skin, liver, kidney and stomach

Langner *et al.* examined the dose response of dermal toxicity in mice dosed with 8-MOP and then irradiated with UVA light. Ten mg/kg with a light dose of 10 minutes (2 J/cm^2) twice weekly for 10 months caused actinic changes in the skin. A dose of 20 mg/kg with a light dose of 10 minutes (2 J/cm^2) twice weekly for eight months caused notable phototoxicity and chronic erythema. Higher doses of drug and light caused significant phototoxicity and extensive inflammatory changes with acute erythema, deep ulcers, and deformities. Doses of 20 mg/kg with a light dose of 10 minutes (2 J/cm^2) six times a week

for 3 months killed some of the mice. The following table shows the temporal progression of skin lesions in this dose group.

Time	Symptom
24 hr	No visible skin changes
48 hr	Minimal erythema and slight edema of the dorsum and head
72 hr	Moderate erythema and edema of the dorsum
96 hr	Prominent erythema and edema, small erosions in over 50% of the mice
5-8 days	Confluence of erosions in the erythematous area of the dorsum and neck
8-14 days	Erosions covered with a crust, lichenification of the skin on the dorsum
14-20 days	Ulcers covered with massive crusts
20 to 40 days	Progressive ulceration and scar formation leading to deformity

This phototoxic dose, 20 mg/kg or 60 mg/m^2, is about 500 times greater than the maximum possible dose proposed in this NDA. It is about 3 times greater than the normal dose for treating psoriases on a mg/m^2 basis.

Doses that caused phototoxicity caused significant differences in the incorporation of ^{3}H-thymidine into epidermal cells. The table below shows that though there was no clear dose response, a dose that caused only minimal phototoxicity caused an apparent increase in cutaneous DNA synthesis.

Dose group	Duration	% epidermal cells labeled		
	Months	Mean	sd	t-test
1 mg/kg no UVA irradiation (Control	12	2.81	0.74	
1 mg/kg + UVA 2X/week for 5 min	10	1.5	0.41	< 0.01
1 mg/kg + UVA 2X/week for 10 min	12	5.65	0.34	< 0.001

Despite the significant damage at the higher dose, and despite the increase in DNA synthesis, prolonged treatment did not cause malignant skin lesions. Other groups have reported the induction of malignant lesions under different conditions, primarily route (see references in this report). Microscopic changes in the skin were dose dependent. They included partial destruction of the epidermis, partial ancanthosis with hyperchromatic nuclei. There was some lymphocyte infiltration. At the end of the experiments, there was dose dependant focal necrosis. There was no microscopic damage in the stomach, kidneys, spleen or stomach. There was some toxic damage to the livers of three mice but this was not obviously dose related. There were no changes in immunofluorescence.

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.

Animal male and female F344/N rats, five per sex per dose group.
Drug 8-MOP
Lot 21335

NDA 20-969

Doses	0, 50, 100, 200, 400, 800 mg/kg (0, 300, 600, 1200, 2400, 4800 mg/m^2)
Schedule	5 days/week for 12 doses over a 16 day period
Formulation	Corn oil
Route	PO Gavage
Observations	
Clinical signs	Daily for two weeks
Body Weight	d0, 7 and 15
Necropsy	End of dosing

This was a GLP Study done by SRI Laboratories.

The following table shows the results of this study. Doses of 200 mg/kg or greater caused the rats to gain less weight than controls over the course of the study. Rats in these higher three dose groups were less active than controls or lower dose animals. No compound related changes were seen at necropsy.

	Dose mg/kg	Survival	Days of death	Change in weight relative to predose weight	Final weight relative to control (%)
Male	0	5/5		75	
	50	5/5		74	99
	100	5/5		63	97
	200	5/5		47	86
	400	4/5	11	-4	70
	800	0/5	3,3,3,3,5		
Female	0	5/5		38	
	50	5/5		31	96
	100	5/5		35	99
	200	4/5	15	11	86
	400	4/5	4	-7	70
	800	0/5	3,3,3,3,3		

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

Animal	male and female F344/N rats, ten per sex per dose group.
Drug	8-MOP
Lot	21335
Doses	0, 25, 50, 100, 200, 400 mg/kg (0, 150, 300, 600, 1200, 2400 mg/m^2)
Schedule	5 days/week for 13 weeks

NDA 20-969
Formulation Corn oil
Route PO Gavage
Observations
Clinical signs Daily
Body Weight d0, weekly
Necropsy End of dosing
Histopathology was studied in the following tissues in the control, 200 mg/kg and 400 mg/kg groups: See table for tissues.

This was a GLP Study.

The following table shows the body weight changes and mortality caused by these doses. Doses of 100 mg/kg or greater caused the rats to gain less weight than controls over the course of the study. Rats in these higher three dose groups were less active than controls or lower dose animals. Relative liver weights increased in all but the low dose groups. The change was as much as 50% in the high dose group. This was probably an induction process.

	Dose	Survival	Weeks of death	Change in weight relative to predose weight grams	Final weight relative to control (%)
	mg/kg				
Male	0	10/10		176	
	25	10/10		194	105
	50	10/10		187	103
	100	10/10		139	88
	200	10/10		99	78
	400	4/10	2,2,2,2,8,9	14	55
Female	0	10/10		78	
	25	10/10		75	100
	50	10/10		74	98
	100	10/10		79	101
	200	10/10		44	85
	400	2/10	1,1,2,2,2,2,2,2	3	65

Compound-related microscopic changes were seen in the liver, adrenal glands, testes, seminal vesicles, and prostate. Minimal to mild fatty changes in the liver were observed in 9/10 males and 10/10 females in the high dose group and in 6/10 males and 8/10 females in the 200 mg/kg group. These fatty changes were not seen in the controls. Fatty changes in the adrenal glands were seen in 7/10 females in the high dose group. Atrophy of the testes, seminal vesicles and prostate were seen in 9/10 male rats in the high dose group and 2/10 males in the 200 mg/kg group.

NDA 20-969

6) A preliminary 2-week tolerance study in dogs with UVADEX and photopheresis using the UVAR Centrinet System. Study Number 2686-101. Volume 8, page 180.

Animal	Two male beagle dogs
Body Wt. Ave	12.8 kg
Drug	UVADEX Liquid (lot no. C162450-01)
Dose	2.8 ml, 20-μg/ml solution (56 μg) per treatment
Route	Extracorporeal. Drug is added to blood (150 ml/cycle) in the Centrinet system. Blood drawn via Jugular Catheter connected to the Centrinet system
Schedule	Days 1, 2, 8, and 9 (four treatments, equivalent to clinical schedule)
UVA light	1 to 2 J/cm^2 in the Centrinet system
Observations	
Clinical Signs	Daily
Body Wt.	Weekly
Clinical Chemistry	Before treatment, day 3, day 10 and at termination
Hematology	Before treatment, day 3, day 10 and at termination
Flow Cytometry	Before treatment and day 10 (24 hr after last treatment)
Lymphocyte viability	Post irradiation whole blood drawn after each treatment before return. White cells were separated by differential centrifugation and cultured for 7 days.
Drug Concentration	Days 1 and 8 10 minutes after final reinfusion of UVADEX treated blood
Necropsy	Day 16
Histopathology	Tissues preserved but not examined.

did this study at their facilities. I did not find a GLP statement.

Results:

Mortality	Both dogs survived to scheduled necropsy
Clinical signs	Swollen area on neck, day 3 both dogs. Soft discolored feces, both dogs day 2.
Body Wt.	No treatment related effects
Food Consumption	No treatment related effects
Hematology	No treatment related effects
Clinical Chemistry	One dog had elevated LDH and CK day 10 and 16 (2X pretreatment)
Flow Cytometry	Decrease in activated T lymphocytes on d10 ~20% (primarily CD-8) Slight increase in B-lymphocytes on d10.
Lymphocyte Viability	The following table shows the results of this test and compares those results to those seen with blood from two control dogs.

	Culture Day				
	Day 0		Day 1	Day 3	Day 7
	Density $X10^{-6}$	Viability %	Viability %	Viability %	Viability %
Control	1.7	94.8	87.4	94.9	76.9
Study Day in treated dogs					
1	1.6	97.5	93.3	56.4	5.9
2	1.3	100.0	98.7	73.0	21.8
8	1.4	98.0	97.4	93.8	28.7
9	2.4	97.5	91.3	88.8	30.3

Drug Concentration — did not do this analysis; they sent the samples to the sponsor. Consequently, they did not include these results in this report.

Gross Pathology — Only incidental findings

During each treatment, the Centrinet system removed 150 ml of blood per cycle for two cycles or a total of 300 ml of blood. If the concentration of UVADEX in this blood is 50 ng/ml (the minimum target concentration) the total dose would be 15 µg. The actual dose was 56 µg or nearly four times the minimum target dose.

This therapy is designed to kill white cells, so the decrease of viability of lymphocytes in culture is not surprising. Nevertheless, it is interesting that the decrease in viability does not begin until the third day in culture. This suggests damage at the gene level.

CD-8 cells attack cells presenting foreign antigens. This attack is radical mediated and suicidal. Thus, the decrease in CD-8 cells may result from the attack of these cells on cells damaged by the photopheresis process. But, the decrease is very rapid. More likely, the decrease results from the generation of excess radicals within the radical generating machinery of the CD-8 cells. The investigators did not do a photopheresis only (no 8-MOP) control.

7) 4-week toxicity study in dogs with UVADEX and photopheresis using the UVAR Centrinet System. Study Number 2686-102. Volume 9, page 222.

Animal — male and female beagle dogs

Body Wt. — Range 5.9 to 9.8 kg for males and 6.7 to 8.1 kg for females

Drug — UVADEX Liquid (lot no. C178093-03)
Methoxsalen placebo (lot no. C172592-02)

Dose — 0, 100 or 500 ng/ml, three dogs per sex per dose group.

Route — Extracorporeal. Drug is added to blood (150 ml/cycle) in the Centrinet system.
Blood drawn via Jugular Catheter connected to the Centrinet system

Schedule — two consecutive days a week, days 1, 2, 8, 9, 15, 16, 22 and 23, for four weeks

Blood Treated — 150 ml per cycle, about 300 ml total

UVA light — 1 to 2 J/cm^2 in the Centrinet system

Observations

Clinical Signs — Twice daily

NDA 20-969

Physical Exam	Before treatment and weekly
Body Wt.	Weekly
Ophthal. Exam.	Before treatment and at the end of the experiment
Blood Pressure	Before treatment and post cycles 1 or 2,
Clinical Chemistry	Before treatment, week 2 and week 4
Hematology	Before treatment, week 2 and week 4
Urinanalysis	Weekly
Flow Cytometry	Before treatment and 18 to 26 hours after the last treatment
Lymphocyte viability	White cells were separated by differential centrifugation and cultured for 7 days.
Drug Concentration	Weekly
Necropsy	After four weeks.
Histopathology	See table for tissues.

did this study at their facilities. Blair Wingard signed the GLP statement.

Results:

Mortality	All dogs survived to scheduled necropsy
Clinical signs	No toxicologically significant effects
Body Wt.	No treatment related effects
Food Consumption	No treatment related effects
Blood Pressure	No treatment related effects
Ophthal. Exam	No treatment related effects
Hematology	Decrease in red cell parameters, Hbg, RBC, Hct most notable in week 4 (about 21%) in all groups. This is associated with repeated blood sampling.
Urinanalysis	No toxicologically significant changes
Clinical Chemistry	No toxicologically significant changes
Flow Cytometry	No toxicologically significant changes
Lymphocyte Viability	A slight reduction in viability was seen in the lymphocytes of animals treated with UVADEX liquid on culture days 3 and 7. This is consistent with the mechanism of the therapy.
Gross Pathology	No toxicologically significant changes
Organ Weights	No toxicologically significant changes
Histopathology	Moderate to severe chronic inflammation, hemorrhage, and degeneration and necrosis at the catheter site in treated and control dogs. Thrombi in the thoracic cavity associated with catheterization.

UVAR CENTRINET treatment causes little toxicity in dogs.

NDA 20-969

8) T Rozman *et al.* 1989. Toxicity of 8-methoxypsoralen in cynomolgous monkeys (Macaca fascicularis). *Drug Chem. Toxicol.* 12(1): 21-37. Volume 10, page 1.

Animal	male (5.5 ± 0.2 kg) and female (3.7 ± 0.1 kg) cynomolgous monkeys (Macaca fascicularis)
Drug	8-methoxypsoralen
Drug Lot	German commercially available drug, Lot number 80M4 and 81ML.
Formulation	"hydroxypropyl-methyl-cellulose gel", 1 ml/kg.
Route	Stomach tube.
Doses	0, 2, 6, or 18 mg/kg (0, 24, 72 or 216 mg/m^2), three per sex per dose group. Three additional males and three females received the highest dose at the same schedule and were allowed to recover for eight weeks after the 26-week dosing period.
Schedule	three times per week (Monday, Wednesday and Friday) for 26 weeks.
Observations	
Clinical Signs	Daily
Body Weight	Before dosing, week 1, 6, 13, 18, and 26, plus 34 for recovery animals.
Food Cons.	Before dosing, week 1, 6, 13, 18, and 26, plus 34 for recovery animals.
Hematology	Before dosing, week 1, 6, 13, 18 and 26, plus 34 for recovery animals.
Clinical Chem.	Before dosing, week 1, 6, 13, 18 and 26, plus week 34 for recovery animals.
Urinalysis	Before dosing, week 1, 6, 13 and 26, plus week 34 for recovery animals.
ECG	Week 1, 6, 13, 18 and 26, plus week 34 for recovery animals.
Blood pressure	End of study
Ophthalmic Exam	End of study
Hearing	End of study
PK Sampling	1, 2, 4, and 8 hr after first dose 1, 2, 4, and 8 hr after first dose of week 13 1, 2, 4, 8, and 24 hours after the last dose of week 26.
Necropsy	Week 26 and Week 34 for recovery animals
Histopathology	See table for tissues

This is a published article and not a study report, the authors did not include a GLP statement.

Results:

Mortality	One female in the highest dose group (intended for recovery) moribund on day 39. All other animals survived to scheduled necropsy. This animal showed signs of shock (severe congestion) in lungs, liver and kidney, involution of the thymus and multiple, globular calcifications of the gonads. This monkey also showed signs of hepatocellular degeneration and regeneration with Kupffer cell proliferation.
Clinical Signs	Dose dependent emesis, none in low dose group, intermittent in mid dose group and regularly in the high dose group.
Body Weight	No statistically significant differences, but a trend toward lower weights in high dose males and females.
Food Cons.	No statistically significant differences

NDA 20-969

Urinalysis	No statistically significant differences
ECG	No statistically significant differences
Blood Pres.	No statistically significant differences
Ophth.	No statistically significant differences
Hearing	No statistically significant differences
Organ weight	No statistically significant differences
Clinical Chem	No toxicologically significant differences
Hematology	No toxicologically significant differences
Necropsy	No toxicologically significant differences
Histopathology	Kupffer cell proliferation in one female control, no low dose animals, 2 male and 2 female mid-dose animals and 3 high dose females.

Pharmacokinetics:

PK parameters showed a lot of variability with no apparent differences between males and females. Also there were no consistent differences at different times during the experiment. The following table shows the AUC values at different times during the experiment. Note the increase between the mid and high-dose is approximately dose proportional but the increase between the low and mid dose group is consistently much greater than dose proportional. This suggests that some process in the GI or liver may be able to dispose of small doses, but not larger doses. The authors state that a saturable first pass effect has been demonstrated in man and rats.

Week of Treatment	Dose		AUC of 8-MOP (µg*h/ml)					
	mg/kg	Factor Increase	Males	sd	Factor Increase	Females	sd	Factor Increase
1	2		0.85	0.57		1.21	0.79	
	6	3	8.5	3.74	10.0	5.74	1.47	4.7
	18	3	18.25	2.23	2.1	15.92	3.14	2.8
13	2		1.11	0.6		1.76	0.65	
	6	3	8.69	1.67	7.8	7.22	1.94	4.1
	18	3	14.15	6.67	1.6	10.01	6.93	1.4
26	2		0.41	0.39		0.21	0.26	
	6	3	8.06	3.41	19.7	5.46	1.86	26.0
	18	3	23.12	3.08	2.9	14.98	7.83	2.7

Mean time to peak concentration was about 1-2 hours at the low dose and 4 to 8 hours at the mid and high-dose.

Discussion:

The low dose, 2 mg/kg, was essentially a NOAEL. The higher doses caused dose dependent emesis. Females seemed to be more sensitive to this toxicity and to the microscopic finding of Kupffer cell proliferation than males. The authors considered the death of the high dose female drug related.

Toxicology Summary:

The single-dose LD_{50} of 8-MOP in rats and mice is approximately 500 mg/kg. The IP LD_{50} is about 200 mg/kg. These values are about the same in both species for both routes so the rat appears to be less sensitive to 8-MOP toxicity on a mg/m^2 basis. Values as high as 2 g/kg for the oral LD_{50} have been reported. This apparent difference probably results when the particle size in the oral dosing suspension is large. This leads to poor absorption and higher apparent LD_{50} values. Rodents dosed with toxic amounts of 8-MOP become hypoactive and ataxic. At higher dose levels, the animals suffer prostration, muscle twitches and convulsions. Most deaths occurred in the first few days after dosing. Evidently, the dose response curve is relatively steep.

Twelve oral doses of 400 mg/kg (2400 mg/m^2) over 16 days killed one of five male rats and one of five female rats. Little or no toxicity occurred in lower dose groups. A dose of 400 mg/kg given five times a week for thirteen weeks killed six of ten males and eight of ten females. Compound-related microscopic changes included fatty changes in liver and adrenal glands, and atrophy in the testes, seminal vesicles, and prostate. The only clinical sign seen in this study was dose dependent decreased weight gain.

Rats dosed up to 75 mg/kg (450 mg/m^2) five days a week for 103 weeks developed significant toxicity. This toxicity was more pronounced in males than in females. Despite the absence of clinical signs and only small changes in mortality, 8-MOP caused significant microscopic damage. The most severe dose dependent damage was in the kidneys. 8-MOP caused a spectrum of degenerative and proliferative changes in the kidneys of male rats. Nephropathy included degeneration and regeneration of the tubular epithelium with dilation and atrophy of the tubules, formation of hyaline and granular casts, thickening of the basement membranes, interstitial fibrosis and glomerulosclerosis and mineralization of the renal papilla.

A dose of 18 mg/kg (216 mg/m^2) given three times per week for 26 weeks rendered one of three female monkeys moribund on day 39. All three males survived this dose. The moribund animal showed signs of cellular congestion in the lungs, liver and kidney, involution of the thymus and multiple, globular calcifications of the gonads. This monkey also showed signs of hepatocellular degeneration and regeneration with Kupffer cell proliferation. Kupffer cell proliferation in the liver was the only sign of toxicity in surviving monkeys.

8-MOP is phototoxic. Ten mg/kg given before a 10 minute light dose (2 J/cm^2) twice weekly for 10 months caused actinic changes in the skin of hairless mice. Doses of 20 mg/kg before a 10 minute light dose (2 J/cm^2) twice weekly for eight months caused notable phototoxicity and chronic erythema. Higher doses of drug and light caused significant phototoxicity and extensive inflammatory changes with acute erythema, deep ulcers, and deformities. Doses of 20 mg/kg with a light dose of 10 minutes (2 J/cm^2) six times a week for 3 months killed some of the mice. In some studies, this photo-damage leads to neoplastic changes. Doses that cause phototoxicity are about three times higher than the human dose for psoriasis on a mg/m^2 basis and about 500 times higher than the maximum doses possible in the current NDA.

Therakos has studied the photopheresis process extensively in dogs with the CENTRINET device. The maximum dose of extra-corporeal 8-MOP they studied was 500 ng/ml or about twice the normal dose used in photopheresis for humans. These studies showed that the photopheresis process causes little toxicity. The mild decreases in white cell parameters seen in some of these experiments result from the phototoxic mechanism of the process. The number of blood-draws required by the experimental protocols probably caused the mild decreases in red cell parameters.

Reproductive Toxicology:

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.

Animal	Female Crl:CD BR VAF/Plus out-bred Sprague-Dawley rats, plus male breeders of the same strain.
Drug	8-MOP, Fluka Chemical Company,
Lot Number	RTI Log No. 5354-162-01
Doses	Vehicle, 20, 80, 120, or 160 mg/kg/day 0, 120, 480, 720, 960 mg/m^2/d
Vehicle	Corn Oil.
Route	PO gavage
Dose Volume	5 ml/kg
Schedule	Gestation days 6 through 15.
Observations:	
Clin Signs	Daily
Body Weight	Gestation day (gd) 0, 3, 6 through 15, 18 and 20
Food Cons.	Gd 0, 3, 6, 9, 12, 15, 18 and 20
Water Cons.	Gd 0, 3, 6, 9, 12, 15, 18 and 20
Maternal	body, liver, and uterine weight, number of corpora lutea, implantations, resorptions, early resorptions, and dead and live fetuses.
Fetuses	Fetal weight, external malformations, visceral examination, skeletal malformations, head examinations in half the animals.
Necropsy	Gd 20

This was a GLP study.

Dose Range Finding Study:

In an earlier study, NTP studied doses of 0, 20, 100, 200, 400, or 600 mg/kg/day given by gavage on days 6 through 15 of gestation to Sprague-Dawley rats. All but one of the dams in the 400 and 600 mg/kg groups died or were moribund before gestation day 17. The one surviving rat in the 400-mg/kg group was not pregnant and survived to necropsy on day 20. Dams in the 200-mg/kg group survived to gd 20 but had rough coats and decreased weight gain. Dams in the 100-mg/kg group also showed decreased weight gain. Twenty-mg/kg caused no maternal toxicity. The mid-dose, 200-mg/kg, caused developmental toxicity.

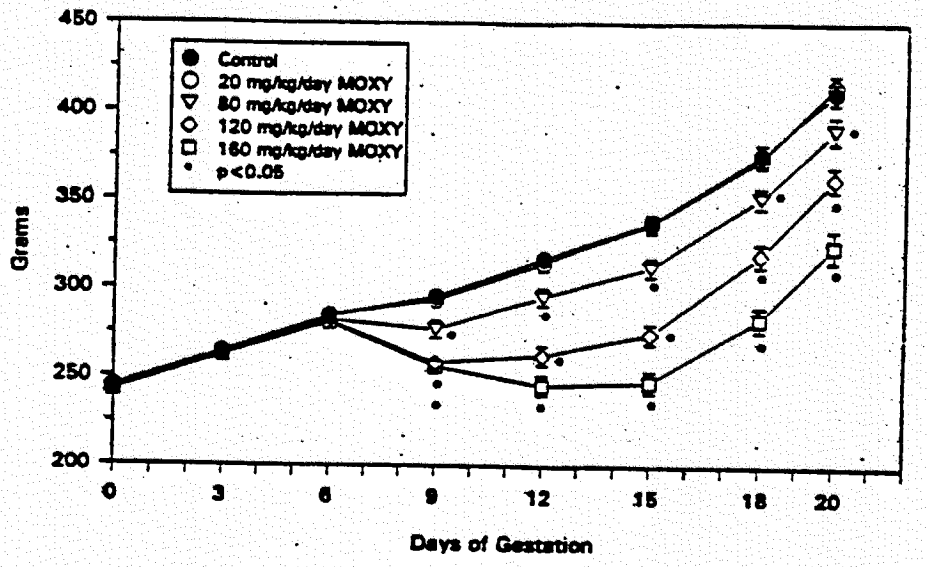
NDA 20-969
Maternal Toxicity:

Mortality	All rats survived to scheduled necropsy
Clinical Signs	Dose related rough coat in 120 and 160 mg/kg groups.
Body Weight	The following table shows that maternal weight decreased with increased dose and with dosing time. Rats also showed even more dramatic decreased weight gain.

Body Weight Changes

Dose Group	Day 9	Day 15
mg/kg/d	% Decrease from control	% Decrease from control
20	0	0
80	6	7.5
120	13	19
160	13	27

Maternal Body Weight Profile



Uterine Wt.	Gravid uterine wt was 15% less than controls in the 120 mg/kg group and 40% less than controls in the 160 mg/kg group.
Liver Wt.	Relative liver weight increased secondary to decreased body weight, 7%, 17% and 26% in the 80, 120 and 160 mg/kg groups respectively.
Food Cons.	Sharp decrease at the beginning of dosing consistent with decreased weights. Recovered after dosing.
Water Cons.	20 and 80 mg/kg groups 11 to 12% decreased between gd 6 and 9. 120 and 160 mg/kg groups 23% decreased between gd 6 and 9.

Rose to equal controls between days 12 and 15.
Significantly elevated in dosed groups during recovery, 31%, 41% and 86% more than controls in the 80, 120 and 160 mg/kg groups respectively between days 18 and 20.

Embryo Fetal Effects.

The following table summarizes the developmental toxicity associated with 8-MOP. The two highest doses caused significant fetal toxicity. Maternal weight loss is associated with significant fetal toxicity. This may account for some or all of the toxicity seen with 8-MOP. The change in body weight clearly shows the dams were stressed. The authors were not certain that the increase in enlarged lateral ventricles was directly associated with dosing. They state that the background incidence of this malformation in their laboratory is highly variable and ranges from 0 to 27%. The incidence in this study is within that range, 24%. Nevertheless, the increase with dose arouses suspicion.

For psoriasis therapy, the average adult takes about 50 mg (30 mg/m^2) of 8-MOP two hours before exposure to UVA light. So the dose that caused no maternal toxicity and only minimal fetal toxicity in this study, 80 mg/kg or 480 mg/m^2, is 16 times greater than the dose recommended for psoriasis therapy. This lowest fetotoxic dose is over 4000 times greater than the maximum re-infused dose in a single course of UVADEX therapy.

dose	0	sem	20	sem	80	sem	120	sem	160	sem
All Litters	22		23		25		23		24	
No corpora lutea per dam	16.2 §	0.3	16.2	0.5	14.6*	0.6	15	0.4	13.7*	0.8
No. implantation sites per litter	15.6 §	0.4	15.9	0.4	14.1	0.8	14.9	0.4	13.6*	0.7
% resorptions per litter	3.6 §	1.2	2.8	1	1.6	0.8	9.1	5.4	23.8*	7.2
% litters with one or more resorption	41		30		16		26		54	
% late fetal deaths per litter	0	0	0	0	0	0	0	0	0.3	0.3
% litters with one or more late fetal deaths	0		0		0		0		4	
% nonlive implants per litter	3.6 §	1.2	2.8	1	1.6	0.8	9.1	5.4	24.1*	7.2
% litters with one or more nonlive implants	41		30		16		26		54	
% litters with 100% nonlive implants	0		0		0		4		13	
% adversely affected implants per litter	4.2 §	1.2	3.5	1.1	6.9	4.2	11.1	5.3	30.4	7.5
% litters with one or more adversely affected implants	45		39		24		43		63	
Live litters	22		23		25		22		21	
No. live fetuses per litter	15.1 §	0.45	15.5	0.5	13.8	0.8	14.2	0.7	12.1*	0.7
Average fetal body wt. (g) per litter										
male fetuses	3.76 §	0.06	3.82	0.06	3.77	0.07	3.54	0.07	3.02*	0.15
female fetuses	3.55 §	0.06	3.64	0.05	3.58	0.05	3.36	0.07	2.87*	0.14
% male fetuses per litter										
Malformations										
% fetuses malformed per litter	0.7 §	0.5	0.7	0.5	5.4	4.1	2	1	10.3	4
male	0.7	0.7	0.7	0.5	5.5	4.1	2.4	1.4	6.3	2.8
female	0.7 §	0.7	0.7	0.7	1.5	1.2	1.4	1	15.5	7.1
% litters with malformed fetuses	9 §		9		16		18		33	
% fetuses with enlarged lateral vetericles per litter	0 §	0	0.5	0.5	0.9	0.7	1.7	1	6.8*	3.2
% lttters with enlarged lateral ventricles	0 ++		4		8		14		24	
Variations										
% fetuses with variations per litter	6.4 §	2.8	8.2	2	9.7	2.5	20.4*	5.6	26.9*	5.4
% litters with one or more variations per litter	41		57		48		77#		86#	

* Significantly different from control p <0.05, Dunnett's or Williams or both tests.
§ Significant in Test for linear trend
++ p < 0.05 test for linear trend on proportions
# significant by Fishers Exact Test

Reproductive toxicity summary:

Doses of 80, 120 and 160 mg/kg/d (480, 720, 960 mg/m^2/d) during gestation caused significant fetal toxicity in rats. This toxicity was strongly associated with maternal weight loss, anorexia and increased relative liver weight. Thus, the fetal toxicity may be a direct consequence of maternal toxicity. Signs of fetal toxicity included increased fetal mortality, increased resorptions, late fetal death, fewer fetuses per litter and decreased fetal weight. Treatment caused an increase in skeletal malformation and

variations. 8-MOP treatment is embryo-lethal and teratogenic at doses ≥ 80 mg/kg/day. This dose caused minimal maternal toxicity.

For psoriasis therapy, the average adult takes about 50 mg (30 mg/m^2) of 8-MOP two hours before exposure to UVA light. So the dose that caused no maternal toxicity and only minimal fetal toxicity in this study (80 mg/kg or 480 mg/m^2) is 16 times greater than the dose recommended for psoriasis therapy. This lowest fetotoxic dose is over 4000 times greater than the maximum re-infused dose in a single course of UVADEX therapy.

Carcinogenicity:

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.

These authors followed 1373 patients given oral 8-methoxypsoralen photochemotherapy for psoriasis prospectively for 2.1 years. Thirty of these patients developed a total of 48 basal-cell or squamous-cell carcinomas. The observed incidence of cutaneous carcinoma was 2.63 (95% confidence limits 1.9 to 3.9) times that expected for an age, sex and geographically matched population. Relative risk to patients with a history of ionizing radiation was 3.66 (99% confidence limits, 2.42 to 8.69). Patients with a previous cutaneous carcinoma had a relative risk of 10.22 (99% confidence limits, 4.78 to 37.08). The researchers observed a higher than expected proportion of squamous-cell carcinomas and an excess of squamous-cell carcinomas in areas not exposed to sun. The authors conclude that new psoriasis patients with histories of ionizing radiation exposure or previous skin tumor should be informed of this increased risk.

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.

Animal	male and female F344/N rats, 50 per sex per dose group.
Drug	8-MOP
Lot	21335 and 21784
Doses	0, 37.5 or 75 mg/kg (0, 225, 450 mg/m^2)
Schedule	Five days per week for 103 weeks
Formulation	Corn oil, dose volume 5 ml/kg
Route	PO Gavage
Observations	
Clinical signs	Daily
Body Weight	d0, weekly for 13 weeks then monthly
Necropsy	End of dosing

Histopathology See table for tissues.

This NTP Technical report is based on the 13-week studies that was done between May and August 1980 and on the two-year studies that began in May 1981 and ended May 1983 at SRI International. It also reports shorter preliminary studies and mutagenicity studies. NTP published the technical report itself in 1989. So the studies I have reviewed here are relatively old. Also, the Technical Report contains only summary data of the various studies; there are no individual animal data or line listings. Thus, this is not a review of a carcinogenicity study report, but only of the technical report. The NTP did not analyze the carcinogenicity data for combined tumor incidence. Evidently, that was not the practice at the time.

Results:

The following Kaplan-Meier graphs show that 8-MOP dosing decreased the probability of survival for both males and females. The decrease in survival was considerably less pronounced in females. In fact in females, the survival of the mid-dose group was worse than that of the high-dose group. Indeed, in females the difference did not reach statistical significance. The reduced survival in males was probably secondary to chronic kidney toxicity (see below).