PHARMACOLOGY

TEST TYPE	SPECIES	DOSE	RESULTS
Therapeutic Activity:			
Effect on transplanted tumors	Female Swiss mouse, Wistar rat	12.5 - 100 mg/kg/day p.o. or i.p.	No inhibitory effect on mouse Ehrlich sarcoma, mouse Ehrlich ascites, sarcoma, mouse Crocker sarcoma S180, mouse leukemia L1210, rat Walker carcinosarcoma 256, rat uterus epithelioma T8 (Guerin)
	C57BL/6 mouse	45 µg/mouse i.p. twice weekly for 3 weeks	Decrease of tumor burden from 2.9 to 1.6% of body weight; antagonism of several tumor-induced immunosuppressive changes
	DBA/2 mouse	1.5 or 15 µg/mouse s.c. daily for 13 days	Enhanced growth of P388 tumors
Effect on chemically induced papillomas	Female Swiss mouse	100 - 400 mg/kg p.o. or i.p. weekly for 2 weeks; 20 or 40 mg/kg/day p.o. for 2 or 6 weeks	Dose-related regression of papillomas induced by dimethylbenzanthracene/ croton oil
Effect on chemically induced skin carcinomas	Female Swiss mouse	400 mg/kg p.o. weekly for 2 weeks	Stabilization or regression in 5 and 11 tumors, respectively
		200 mg/kg p.o. every 2 weeks during promotion phase	Delay of tumor induction; reduced incidence of tumors induced by dimethylbenzanthracene/croton oil
Effect on chemically induced bladder tumors	Wistar-Lewis rat	2.5 or 5 mg/kg diet for 37 weeks	Significant reduction in incidence of papillary tumors of bladder induced by N-methyl-N-nitrosourea
Effect on cell growth/ differentiation (in vitro study)	Human head/neck squamous carcinoma spheroids	10^{-10} to 10^{-6}M (0.3 ng/mL to 3 µg/mL)	Dose-relation inhibition of growth and expression of differentiation markers
Effect of cell proliferation (in vitro study)	Human cell lines HL60 (acute myeloid leukemia), MCF-7 (mammary carcinoma) SCC4, SCC15, A431 (squamous cell carcinoma)	3×10^{-9} to 3×10^{-5}M tretinoin (90 ng/mL to 90 µg/mL) alone or combined with interferon-alpha	Dose-related inhibition of proliferation; interferon enhanced effects of tretinoin on cells
Effect on cell differentiation (in vitro study)	HL60 human myeloid leukemia cells	10^{-9} to 10^{-6}M (3 ng/mL to 3 µg/mL)	Dose-related induction of cell differentiation
	Human leukemia cell line HL60, THP-1, U937	10^{-9} to 10^{-6}M (30 ng/mL to 3 µg/mL) tretinoin alone or combined with PGE2	Induction of cell markers of differentiation in all cell lines; additive effect in presence of PGE2
	U937 myelomonocytic leukemia cells	10^{-9} to 10^{-6}M (3 ng/mL to 3 µg/mL) tretinoin alone or combined with cAMP-inducing agents	Dose-related induction of differentiation; tretinoin activity increased by cAMP-inducing agents.

TEST TYPE	SPECIES	DOSE	RESULTS
Effect on cell differentiation (in vitro study) (cont'd)	Human HL-60 (acute myeloid leukemia) and U937 (histiocytic lymphoma) cell lines	10^{-5}M (30 µg/mL) tretinoin alone or combined with interferon alpha/gamma, granulocyte stimulating factor, interleukin-alpha, interleukin 4, tumor necrosis factor alpha	Induction of differentiation in both cell lines; addition of cytokines caused synergistic effects
Mechanism of Action:			
Characterization of cellular retinoid binding protein (in vitro study)	Wide variety of species and tissues	3 x 10^{-11} to 2.5 x 10^{-7}M (0.09 ng/mL to 0.75 µg/mL	Affinity of cellular retinoid binding protein
	HBV positive hepatocellular carcinoma and other tissues	2.5 x 10^{-8} to 3 x 10^{-6}M (75 ng/mL to 9 µg/mL)	Induction of CAT gene expression at physiological concentrations
	cDNA library from human testis, breast cancer (MCF7, T47D) cell lines	10^{-12} to 10^{-6}M (3 pg/mL to 3 µg/mL)	Dose-related induction of CAT gene expression
	RXR-alpha derived by gene expression	10^{-7} (0.3 µg/mL)	Enhanced RAR activity at tretinoin levels not activating RXR-alpha
	RXR derived by gene expression	10^{-5}M (30 µg/mL)	RXR has central role in tretinoin signalling pathway
	Laboratory constructs of RXR, RAR	10^{-9} to 3 x 10^{-6}M (3 ng/mL to 90 µg/mL)	Low tretinoin binding affinity for RXR-alpha; isomerization to 9-cis retinoic acid produced high binding affinity ligand
	Cells from acute promyelocytic leukemia patients	10^{-9}M (3 ng/mL)	RAR-alpha gene in 6/8 patients was translocated to chromosome 15
		not reported	RARmyl and mylRAR fusion transcripts found in acute promyelocytic leukemia; chimeric protein has altered transcriptional activation properties
	NBA cell line (acute promyelocytic leukemia)	not reported	Chimeric promyelocytic leukemia -RAR-alpha protein retains binding domains of RAR-alpha
	AML3 cells from acute promyelocytic leukemia patients	not reported	RAR-alpha gene rearranged as a result of t(15;17) translocation
		10^{-9} to 10^{-5}M (3 ng/mL) to 30 µg/mL)	Increased level of RAR-alpha expression
Level of expression of cellular retinoic acid binding protein (CRABP; in vitro study)	Laboratory constructs of CRABPII, RXR, RAR	10^{-2}M (0.03 mg/mL)	Expression of CRABPII in presence of RXR but not RAR
General Pharmacodynamics:			
Central nervous system effects	Mouse, rat	100 mg/kg p.o.	Slight locomotor depression; no effect on hexobarbital narcosis, placing/grasping reflex

TEST TYPE	SPECIES	DOSE	RESULTS
Cardiovascular and respiratory effects	Dog, cat	up to 1,000 mg/kg p.o.; 0.1 - 10 mg/kg i.v.	No effects at oral doses or at i.v. doses up to 1 mg/kg; at 10 mg/kg, biphasic effects on blood pressure, biphasic effects on respiration, slight bradycardia; similar effects produced by vehicle
Immune system effects	C57BL/6 mouse	50, 100 mg/kg i.p.	No effect on cytotoxicity response to administration of P185x2 mastocytoma cells
		0.05 or 0.1 mg/mouse/ day (approximately 2.8 or 5.5 mg/kg/day) p.o. for 7 days	Stimulation of antibody production against sheep red blood cells or dinitrophenylaminoethyl- carbomylm ethyl-Ficoll; no effect on immunosuppression caused by cyclophosphamide or cyclosporin A
		25, 100, 300, 800 µg/mouse i.p. (approximately 1.25, 5, 15, 40 mg/kg) daily for 5 days	Stimulation of cell-mediated toxicity after challenge with S194 myeloma cells
		100 µg/mouse (approximately 5, 1.25 mg/kg) i.p. daily for 5 days	Decreased deaths from leukemia after exposure to ^{60}Co radiation
		25, 100, 300 µg/mouse i.p. (approximately 1.25, 5, 15 mg/kg) daily for 5 days prior to challenge, then daily for 1 week and 3 times weekly thereafter	Significant inhibition of tumor (EL4) growth, but no cure
	C57BL/6, Balb/c mouse	25, 100, 300 µg/mouse/ day (approximately 1, 4, 12 mg/kg/day for 7 days)	Stimulation of T-killer cell induction in response to S194 myeloma cells; no enhancement of proliferative response in mixed lymphocyte culture; no stimulation of lymphocyte response to mitogens
		5, 25, 100, 300 µg/mouse i.p. (approximately 0.25, 1.25, 5, 15 mg/kg) daily for 5 days, then 3 times weekly for 2 weeks	Dose-related inhibition of tumor growth in 3 of 7 tumor models (S91, L33, E14 cells); effect most marked in strongly immunogenic tumors
		5, 25, 100, 300 µg/mouse i.p. (approximately 0.25, 5, 15 mg/kg) daily for 5 days or 3 times weekly for 1 - 3 months	Stimulation of cell-mediated toxicity using allogeneic (S194) or syngeneic (E14, S194) tumor transfer
	C57BL/6J and BDF1 mouse	50, 100 mg/kg/day i.p. x 4 days	No effect on rejection of C57BL/6J spleen cells transplanted to BDF1 mice
	(C57BL/6J x C3H/eB) F1 mouse	3.3, 33, 330, 3330 µg injected into footpad	Adjuvant effect on immune response

TEST TYPE	SPECIES	DOSE	RESULTS
Immune system effects (cont'd)	Balb/c mouse	10, 30, 100, 300, 1,000 µg/mouse i.p. (approximately 0.5, 1.5, 5, 15, 50 mg/kg) daily for 6 days prior to challenge	Enhancement of neutralizing activity of Balb/c anti-m-KSA immune spleen cells against m-KSA
	BDF1 mouse	100 mg/kg i.p.	No effect on mitogenic response to phytohemagglutinin or concanavalin A administered 1-25 days after tretinoin
	Füllinsdorf mouse	100, 200 mg/kg/day p.o. x 4 days;50, 100, 200 mg/kg/day i.p. x 4 days	No constant effect on IgG titre in response to sheep RBC or lipoplysaccharide
	Lewis rat	5, 150, 300 mg/kg on day 9 - 11 after immunization	Dose-related inhibition of neurological signs of experimental allergic encephalomyelitis
Immune system effects (in vitro study)	Human lymphocytes	1 - 15 µg/mL	Dose-related enhancement of mitogenic effects of phytohemagglutinin or rabbit -antihuman-thymocyte globulin; no effect on conconavalin A or pokeweed mitogen
	Human peripheral mononuclear cells	10^{-7} to 10^{-5}M (0.3 µg/mL to 30 µg/mL) cells	No increase in natural killer cell activity in response to K562, KG-1, MOLT-4, SK-N-SH, and LA-N-5 cells
Lipid metabolism effects	Füllinsdorf rat	1, 10 mg/kg twice daily for 5 doses	Dose-related increase in plasma triglycerides
	Sprague-Dawley rat	33 µg/g diet daily for 28 days; 33 µg/g diet once weekly; 230 µg/g diet once weekly; all animals received 1% cholesterol in diet	Daily dosing increased serum triglycerides; weekly dosing decreased total liver cholesterol and serum cholesterol
		100 µg/g diet for 3 days	2-fold increase in VLDL-triglyceride secretion rate
		105, 210, 315 µg/g diet daily for up to 8 days	Hypertriglyceridemia at all dose levels
		100 µg/g diet for 3 days	Increase in VLDL and HDL lipoproteins; no effect on serum cholesterol
		105 µg/g diet daily for 1 or 28 days; 735 µg/g diet once weekly for 28 days; all animals on 1% cholesterol diet	Increase in serum triglycerides; decrease in serum/liver cholesterol levels; effects reversible
	Wistar rat	5 mg/rat (approximately 70 mg/kg) daily for 2 days	Inhibition of liver lipid changes induced by protein deficiency
	Rabbit	16 mg (approximately 5 - 6 mg/kg) p.o. 3 times weekly for 70 days	Inhibition of atheroma formation in animals on a high cholesterol diet
Other effects - vitamin E absorption	Sprague-Dawley rat	4 mg/kg diet for up to 68 days	Reduction of plasma tocopherol levels due to decreased absorption

TEST TYPE	SPECIES	DOSE	RESULTS
Other effects - vitamin E absorption (cont'd)	Rat	4 mg/kg diet for up to 28 days	0.2% taurocholic acid in diet antagonized inhibition of tocopherol absorption by tretinoin
Other effects - hypervitaminosis D	Wistar rat	21.3 mg/kg/day p.o. for 3 days	Reduced severity of nephrocalcinosis and reduced calcium loss from bone due to 7.5 mg/kg cholecalciferol; no effect on hypercalcemia
Other effects - vitamin A deficiency	Rat	40 µg/rat/day for 5 - 13 days	Partial reversal of percent cornified cells in vagina; irregular mating patterns; no or slight effect on serum progesterone levels in vitamin A deficient animals
		40 µg daily (approximately 0.2 mg/kg) for 30 days prior to surgery, 250 µg (approximately 1.25 mg/kg) on day 1 post-surgery, then 100 µg/day (approximately0.5 mg/kg)	Markedly lower increase in liver weight in tretinoin treated vitamin A deficient animals
		0.1 to 3 mg/day in diet or twice weekly dosing	Resorption of all fetuses in pregnant vitamin A deficient animals
	Sprague-Dawley rat	5 µg/rat i.p. (approximately 0.025 mg/kg)	Differentiation of vaginal epithelium in vitamin A deficient animals
		10 mg/kg diet for 21 or 29 days	Qualitatively normal but quantitatively subnormal spermatogenesis in vitamin A deficient animals
		0.1 mg p.o.	Activation of protein synthesis in 111 of 698 testicular proteins
	Wistar rat	5 mg/kg diet for 5 mg i.p. once or twice daily	Full development of sperm cells in vitamin A deficient animals
	Holtzman rat	50 µg p.o. 3 times weekly for 15 weeks	No reversal of uterine metaplasia due to vitamin A deficiency
Drug Interactions:			
Aspirin	Swiss mouse	30 mg/kg tretinoin i.p. daily for 21 days with and without aspirin 150 mg/kg p.o.	Reduction of tretinoin mortality; no effect on incidence of fractures
NSAIDS	Swiss mouse	14 mg/kg tretinoin i.p. daily for 21 days alone or in combination with nonsteroidal anti-inflammatory drugs (NSAIDS)	NSAIDS significantly reduced the incidence of tretinoin-induced fractures
Ketoconazole	Wistar rat	200 ng (^{3}H) - tretinoin i.v. after pretreatment with ketoconazole	Ketoconazole inhibited formation of tretinoin metabolites

TEST TYPE	SPECIES	DOSE	RESULTS
Various agents	Wistar rat	0.1 mg/kg tretinoin i.v. after oral administration of ketoconazole, R75251, aminogluethimide, cimetidine, itraconazole, metyrapone, saperconazole	Ketoconazole and R75251 increased tretinoin plasma levels; other agents had no effect

TOXICOLOGY

ACUTE TOXICITY:

SPECIES	ROUTE	OBSERVATION PERIOD	LD_{50} (mg/kg)
Mice	p.o.	24 hours 10 days 14 days	> 4,000 2,200 - 2,600 4,850
	i.p.	24 hours 10 days 14 days	> 4,000 790 - 1,230 520
Rats	p.o.	24 hours 7 days 10 days	> 4,000 7,100 2,000
	i.p.	24 hours 7 days 10 days	> 4,000 385 790
Neonatal Rats	p.o.	5 days	225
Rabbits	p.o.	14 days	> 2,000

Symptoms noted in the mice and rats included sedation, hair loss, respiratory depression, blood-encrusted eyes, swollen eyelids, changes in skin texture, cachexia, diuresis, diarrhea and salivation.

LONG-TERM TOXICITY:

SPECIES	DOSE	ROUTE & DURATION	RESULTS
Subchronic Toxicity:			
Füllinsdorf Mouse	400 mg/kg/day	p.o. x 4 days	100% lethality
C57BL/6, BALB/c Mouse	0.3, 1 mg/mouse (approximately 12, 40 mg/kg/day)	7 days	Decreased thymus weight at low dose; at high dose, decreased thymus, spleen weight, 20% loss of body weight
Swiss Mouse	10, 30, 60, 100 mg/kg/day or 3, 6, 10, 30, 60 mg/kg/day	p.o. or i.p. x 21 days	LD_{50} 31 mg/kg i.p.; 23% mortality at high oral dose; bone fractures at doses >10 mg/kg p.o. or >3 mg/kg i.p.
Wistar Rat	21.3 mg/kg/day	p.o. 3 days	Glomerular hyperemia, glomerular edema, tubular cell degeneration
Rat	0.78, 1.56, 3.12, 6.25, 12.5 mg/kg/day	p.o. x 11 days	Death after 5 days at high dose; decreased weight gain at all doses; slight decrease in hematocrit; bone fractures at 1.56 mg/kg or higher
	46.4, 100, 215, 464 mg/kg/day	p.o. x 11 days	No mortality or pathology at two lowest doses, 2/10 dead after 11 - 12 days at 215 mg/kg; 8/10 dead after 6 - 14 days at 464 mg/kg; bone changes at both doses
	10 mg/rat/day (approximately 50 mg/kg/day)	p.o. 14 days	Elevations in serum alkaline phosphatase and transaminases
Wistar Rat	15 mg/kg/day	p.o. x 4 weeks	Reduced body weight gain, bone fractures, decrease in red blood cells, hemoglobin hematocrit, albumin; increase in cholesterol, alkaline phosphatase, alpha/beta globulins
Sprague-Dawley Rat	0.5, 2, or 5 mg/kg/day	p.o. for 4, 8, or 12 weeks	Dose-related decrease in serum albumin, increased serum alkaline phosphatase
CFN Rat	0.24, 1.2, 6 mg/kg	p.o. x 12 weeks	At two highest doses, increased liver weight and increased serum alkaline phosphatase
Rat	2, 6, 20 mg/kg/day	p.o. x 13 weeks; gelatin beadlet formulation	Bone fractures and poor tolerance at high dose after 2 - 3 weeks; at lower doses, hyperplasia of blood-forming elements, slight increase in liver Kupffer cells, thinning of epidermis
	0.4 or 10 mg/kg/day	p.o. x 90 days	At high dose, increased alkaline phosphatase, decreased albumin; decreased cholesterol

SPECIES	DOSE	ROUTE & DURATION	RESULTS
Sprague-Dawley Rat	1, 4, 14, or 50 mg/kg/day	p.o. x 13 weeks	High dose not tolerated; anemia, depressed growth, increased serum alkaline phosphatase, bone fractures, testicular degeneration at 14 mg/kg/day; decreased haematocrit/ red blood cells, increased alkaline phosphatase at 4 mg/kg/day; decreased haematocrit in females at 1 mg/kg/day
Guinea Pig	10 or 50 mg/kg/day	i.p. x 4 days	Dose-related renal changes - tubular dilation, basophilia, mineralization, glomerular adhesions
Dog	3, 10, 30 mg/kg/day	p.o. x 13 weeks	At 30 mg/kg/day, decreased body weight gain, subacute eczema, acanthotic proliferation of epidermis, spermatogenesis, atrophy of testicular tubular epithelia, hyperplasia of blood-forming elements in marrow; no mortality
Chronic Toxicity:			
Rat	2.5 mg/kg or 5 mg/kg diet	diet - 310-440 days or 191 days	Testicular degeneration

TERATOLOGY AND REPRODUCTION:

SPECIES	DOSE ROUTE & DURATION	RESULTS
Segment I Study:		
Füllinsdorf Rat	0, 0.5, 2, 5 mg/kg p.o. to males for 10 weeks before/during mating; to females 2 weeks before mating and throughout gestation/lactation	No effect on fertility or reproductive capacity; increased mortality of offspring in 5 mg/kg group; no malformations noted
Segment II Study:		
Füllinsdorf Mouse	1, 3, 9, 17, 43, 86, 130 mg/kg p.o. during gestation days 8 - 10	Dose-related teratogenicity; resorption of all fetuses at 9 mg/kg or higher; maternal toxicity at doses above 3 mg/kg
	0, 1, 3, 10 mg/kg s.c. on gestation days 7 - 16	Skeletal abnormalities at 3 and 10 mg/kg; maternal toxicity, fetal resorptions, and no viable offspring at high dose
	0, 0.7, 2, 6 mg/kg/day p.o. on gestation days 7 - 16	Dose-related teratogenicity at 2 and 6 mg/kg/day; slight embryotoxicity, but all offspring died at 6 mg/kg/day; no maternal toxicity
NMRI Mouse	5 - 30 mg/kg p.o. for 3 doses 6 hours apart on gestation day 8	Dose-related incidence of spina bifida aperta and embryolethality
ICR Mouse	25 - 200 mg/kg p.o. on gestation days 9, 10, or 11	Increased incidence of polydactyly; no clear dose-response
CD-1 Mouse	80 mg/kg p.o. on gestation day 9	Teratogenicity (spina bifida, tail defect, craniofacial defect)

A/Jax Mouse	50 - 200 mg/kg p.o. on gestation days 8, 9 or 10	Embryotoxicity at 50 mg/kg; teratogenicity and embryolethality at higher doses
Looptail Mouse	5 mg/kg i.p. on gestation day 8	Neural tube defects
Long – Evans Rat	5 or 10 mg/rat/day p.o. on gestation days 9 - 11 or 8 - 10	89 - 95% embryolethality when given on gestation days 9 - 11; 5% teratogenicity at low dose given on gestation days 8 - 10
Füllinsdorf Rat	0, 2, 5, 10 mg/kg/day s.c. from gestation days 7 to 16	Dose-related teratogenicity; no effect on offspring at 2 and 5 mg/kg/day; low birth weight and 50% mortality during lactation period at high dose
Sprague-Dawley Rat	a) 25 mg/kg p.o. on gestation days 6, 7, 8, 9, 10, 11 or 12;	a) Peak resorption rate on gestation day 9;
	b) 3 - 25 mg/kg p.o. on gestation day 9	b) Dose-related embryolethality; LD_{50} 12.3 mg/kg
	10 - 40 mg/kg i.p. on gestation day 8.5 - 9	Maxillofacial malformations; higher doses caused fetal resorption
	5 mg/kg p.o. on gestation days 8 - 10, 11 - 13, 14 - 16; 2.5 or 5 mg/kg p.o. on gestation days11 - 13 or 14 - 16; 2, 4, or 6 mg/kg p.o. on gestation days 14 - 16	Significant postnatal mortality after 5 mg/kg on gestation days 11 - 13; behavioral changes in offspring exposed to 4 - 6 mg/kg/day
Golden Syrian Hamster	7 - 116 mg/kg p.o. on gestation days 1 - 13	Dose and time-related teratogenicity and embryolethality; peak effect on gestation day 7
Füllinsdorf Rabbit	0, 0.7, 2, 6 mg/kg/day p.o. on gestation days 7 - 19	Teratogenicity and significant increase in resorptions at 6 mg/kg/day; no evidence of skeletal abnormalities nor maternal toxicity
	0, 0.5, 1, 2 mg/kg/day s.c. during gestation days 7 to 19	Slight reduction in maternal weight gain, increased resorptions, reduced fetal weight and survival at 1 and 2 mg/kg/day; teratogenicity at high dose
Rabbit	5, 15, 25, 75 mg/kg/day p.o. during gestation days 7 - 19	Doses of 25 and 75 mg/kg/day not tolerated; all fetuses aborted on day 19 at 15 mg/kg/day; at 5 mg/kg/day, teratogenicity in 1/24 fetuses; 14/24 fetuses did not survive 24-hour
Cynomolgus Monkey	5, 10, 20 mg/kg/day once daily during gestation days 19 - 20 and twice daily on gestation days 21 -24	Dose-dependent embryotoxicity; teratogenicity at 10 mg/kg/day; maternal toxicity at 10 - 20 mg/kg/day
Pigtail Monkey	a) 7.5 or 10 mg/kg/day p.o. on gestation days 18 - 44;	a) High frequency of craniofacial musculoskeletal malformations;
	b) 25 - 40 mg/kg for 2 - 15 days	b) No malformations but 5/19 aborted fetuses
Rhesus Monkey	20 or 40 mg/kg/day between gestation days 17 and 45 for 4 - 8 days	Gestation days 24 - 35 most sensitive for teratogenicity
Rhesus Monkey	a) 20, 40 or 80 mg/kg on gestation days 20, 21 or 22;	a) No embryotoxicity;
	b) 30, 40 or 80 mg/kg/day for 3 days during gestation days 21 - 28	b) Abortion, teratogenicity

Segment III Study:		
Füllinsdorf Rat	0, 2, 5, 10 mg/kg/day p.o. from gestation day 16 to postnatal day 22	Slight inhibition of maternal weight gain at high dose; slight reduction (-12 to 16%) in survival of offspring; no functional or behavioral change in offspring

MUTAGENICITY:

SPECIES	ROUTE & DURATION	RESULTS
S. typhimurium TA1535, TA1537, TA98, TA100	4, 8 mcg/plate with and without metabolic activation; 8 mcg/plate with/without UV exposure	No mutagenicity noted

CARCINOGENICITY:

SPECIES	ROUTE & DURATION	RESULTS
SENCAR Mouse	0.3, 3, 30 µcg/g diet for 44 weeks	Absence of carcinomas at high dose; no effect on incidence of papillomas induced by 7, 12 dimethyl-benz[a]anthracene + 12-0-tetradecanoyl-phorbol-13-acetate
B6D2F1 Mouse	30 mg/kg diet for 12 months	Increased incidence of diethylnitrosamine-induced liver tumors; tretinoin alone had no effect