

Reproductive Tumors in NTP Bioassays

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Target Organs for Workshop

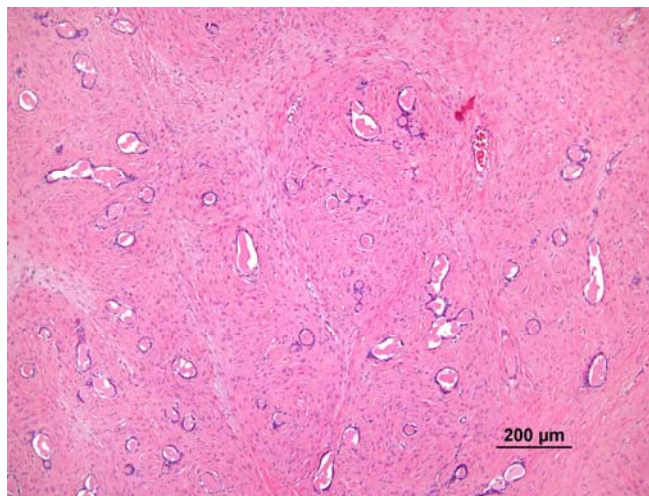
- Mammary gland
- Ovary
- Prostate
- Testis
- Uterus
- Preputial gland

Historical Control Incidences

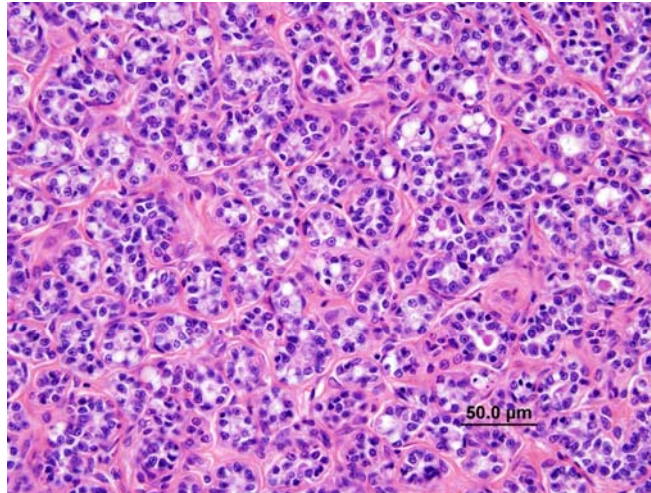
Mammary Gland Neoplasia in Rats

MAMMARY NEOPLASIA § Inhalation Studies				MAMMARY NEOPLASIA § Feed Studies			
----- NIH-07 Diet -----				----- NIH-07 Diet -----			
Rat (F344)	Adenoma	13/1052	1.2%	Rat (F344)	Adenoma	23/1001	2.3%
	Carcinoma	71/1052	6.8%		Carcinoma	32/1001	3.2%
	Ad or Ca	83/1052	7.9%		Ad or Ca	54/1001	5.4%
	Fibroadenoma	421/1052	40%		Fibroadenoma	431/1001	43%
----- NTP-2000 Diet -----				----- NTP-2000 Diet -----			
Rat (F344)	Adenoma	1/499	0.2%	Rat (F344)	Adenoma	4/510	0.8%
	Carcinoma	40/499	8.0%		Carcinoma	9/510	1.8%
	Ad or Ca	41/499	8.2%		Ad or Ca	13/510	2.5%
	Fibroadenoma	210/499	42%		Fibroadenoma	237/510	46%

Mammary Gland Fibroadenoma



Mammary Gland Fibroadenoma



Historical Control Incidences

Mammary Gland Neoplasia in Mice

MAMMARY NEOPLASIA - Inhalation Studies				MAMMARY NEOPLASIA - Feed Studies			
----- NIH-07 Diet -----				----- NIH-07 Diet -----			
B6C3F1	Adenoma	0/1077		B6C3F1	Adenoma	2/953	0.2%
	Carcinoma	25/1077	2.3%		Carcinoma	2/953	0.2%
----- NTP-2000 Diet -----				----- NTP-2000 Diet -----			
B6C3F1	Adenoma	0/450		B6C3F1	Ad or Ca	4/953	0.4%
	Carcinoma	0/450			Myoepithelioma	1/493	0.1%
----- NTP-2000 Diet -----				----- NTP-2000 Diet -----			
	Ad or Ca			B6C3F1	Adenoma	0/510	
					Carcinoma	0/510	
					Ad or Ca		

Chemicals Associated with Mammary Gland Neoplasia in Rats

- | | |
|---|--|
| <ul style="list-style-type: none"> • 2,2-Bis(bromomethyl)-1,3-propanediol * • Chloroprene # • Cytembena • 2,4-Diaminotoluene • 1,2-Dibromo-3-chloropropane • 1,2-Dibromoethane # • 1,2-Dichloroethane # • 3,3'-Dimethoxybenzidine HCl • 3,3'-Dimethylbenzidine HCl • 2,4-Dinitrotoluene • Glycidol * # • Hydrazobenzene • Isophosphamide | <ul style="list-style-type: none"> • Isoprene * • Methylene chloride * • Nithiazide • 5-Nitroacenaphthene • Nitrofurazone • Nitromethane • O-Nitrotoluene * • Ochratoxin A • Phenesterin • Procarbazine HCl • Sulfallate # • 2,4 & 2,6-Toluene diisocyanate • O-Toluidine HCl • 1,2,3-Trichloropropane |
|---|--|

* Mammary gland neoplasia
in both sexes

Mammary gland neoplasia
in female mice

Chemicals Associated with Mammary Gland Neoplasia in Mice

- | | |
|---|--|
| <ul style="list-style-type: none"> • Benzene • 1,3-Butadiene • Choroprene # • 1,2-Dibromoethane # • 1,2-Dichloroethane # • Ethylene oxide • Furosemide • Glycidol #!!! • Reserpine • Sulfallate # • Urethane | <p># Mammary gland neoplasia
in female rats</p> <p>#!/ MAMMARY GLAND NEOPLASIA
in male & female rats</p> |
|---|--|

Principal Non-neoplastic Mammary Lesions Seen in NTP Bioassays

- Hyperplasia
 - Rats > Mice
- Inflammation
 - Rats > Mice
- Galactocele
- Ectasia
- Cyst

Target Organs for Workshop

- Mammary gland
- Ovary
- Prostate
- Testis

Historical Control Incidences

Ovarian Neoplasia in Rats

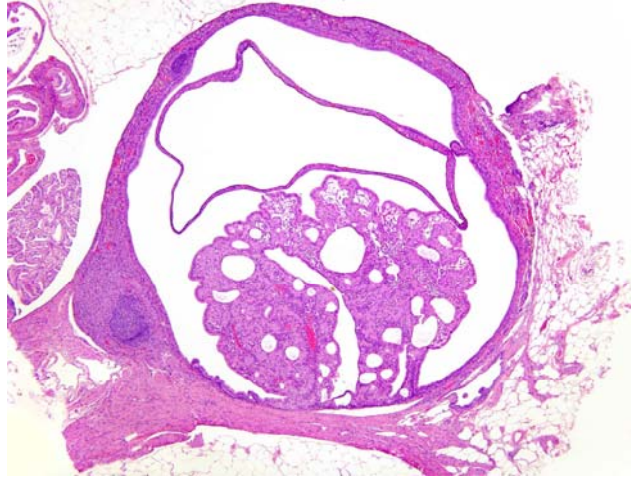
OVARIAN NEOPLASIA - Inhalation Studies			
----- NIH-07 Diet -----			
Rat (F344)	Granulosa cell tumor	9/1050	0.9%
	Granulosa-theca tumor	3/1050	0.3%
	Sex cord stromal tumor	1/1050	0.1%
----- NTP-2000 Diet -----			
Rat (F344)	Granulosa cell tumor	7/499	1.4%
OVARIAN NEOPLASIA - Feed Studies			
----- NIH-07 Diet -----			
Rat (F344)	Adenoma	1/1000	0.1%
	Granulosa cell tumor	10/1000	1.0%
	Granulosa-theca tumor	1/1000	0.1%
	Luteoma	2/1000	0.2%
	Tubulostromal adenoma	1/1000	0.1%
----- NTP-2000 Diet -----			
Rat (F344)	Granulosa cell tumor	0/510	

Historical Control Incidences

Ovarian Neoplasia in Mice

OVARIAN NEOPLASIA - Inhalation Studies				OVARIAN NEOPLASIA - Feed Studies				
----- NIH-07 Diet -----				----- NIH-07 Diet -----				
B6C3F1	Adenoma	3/1055	0.3%	B6C3F1	Adenoma	6/927	0.6%	
	Arrhenoblastoma	2/1055	0.2%		Cystadenoma	18/927	1.9%	
	Cystadenoma	26/1055	2.5%		Fibrous histiocytoma	1/927	0.1%	
	Granulosa cell tumor	6/1055	0.6%		Granulosa cell tumor	6/927	0.6%	
	Hemangioma	3/1055	0.3%		Granulosa-theca tumor	1/927	0.1%	
	Luteoma	6/1055	0.6%		Hemangioma	2/927	0.2%	
	Teratoma	5/1055	0.5%		Luteoma	3/927	0.3%	
	Thecoma	2/1055	0.2%		Teratoma	6/927	0.6%	
	Tubulostromal adenoma	2/1055	0.2%		Thecoma	1/927	0.1%	
	Yolk sac carcinoma	2/1055	0.2%					
----- NTP-2000 Diet -----				----- NTP-2000 Diet -----				
B6C3F1	Cystadenoma	15/436	3.4%	B6C3F1	Cystadenoma	14/503	2.8%	
	Granulosa cell tumor	1/436	0.2%		Granulosa cell tumor	6/503	1.2%	
	Hemangioma	2/436	0.4%		Hemangioma	2/503	0.4%	
	Luteoma	4/436	0.9%		Hemangiosarcoma	1/503	0.2%	
				Luteoma	5/503	1.0%		

Ovarian Cystadenoma



Chemicals Associated with Ovarian Neoplasia in Mice

- Benzene
- 1,3-Butadiene
- N-Methylolacrylamide
- 5-Nitroacenaphthene
- Nitrofurantoin
- Nitrofurazone
- Phenolphthalein
- Urethane
- 4-Vinylcyclohexene
- 4-Vinyl-1-cyclohexene diepoxide

Target Organs for Workshop

- Mammary gland
- Ovary
- Prostate
- Testis

Historical Control Incidences

Prostate Neoplasia in Rats and Mice

PROSTATE NEOPLASIA § Inhalation Studies

----- NIH-07 Diet -----			
Rat (F344)	Adenoma	4/1052	(0.4%)
	Carcinoma	1/1052	(0.1%)
	Ad or Ca	5/1052	(0.5%)

----- NTP-2000 Diet -----

Rat (F344)	Adenoma	1/499	(0.2%)
	Carcinoma	0/499	
	Ad or Ca	1/499	(0.2%)

PROSTATE NEOPLASIA § Feed Studies

----- NIH-07 Diet -----			
Rat (F344)	Adenoma	4/499	(0.4%)
	Carcinoma	0/499	
	Ad or Ca	4/499	(0.4%)

----- NTP-2000 Diet -----

Rat (F344)	Adenoma	8/509	(1.6%)
	Carcinoma	0/509	
	Ad or Ca	8/509	(1.6%)

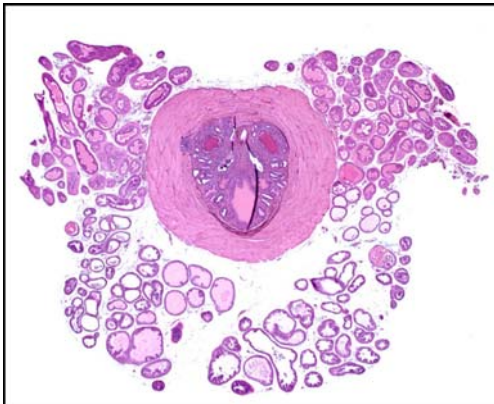
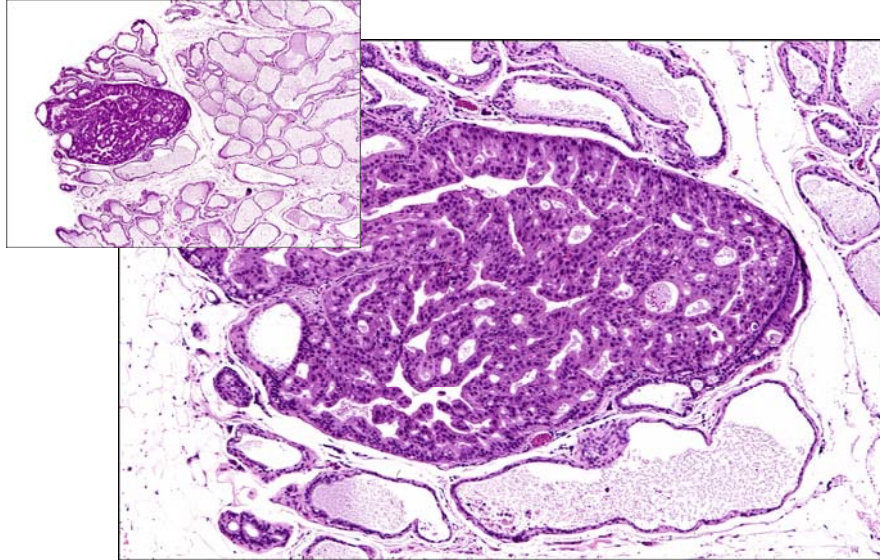
PROSTATE NEOPLASIA § Inhalation Studies

----- NIH-07 Diet -----		
Mouse (B6C3F1)	Adenoma	0/1035
	Carcinoma	0/1035
	Ad or Ca	0/1035

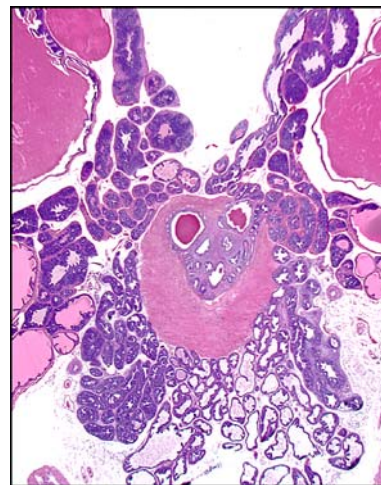
PROSTATE NEOPLASIA § Feed Studies

----- NIH-07 Diet -----		
Mouse (B6C3F1)	Adenoma	0/944
	Carcinoma	0/944
	Ad or Ca	0/944

Prostate Adenoma in a Rat



Wild Type

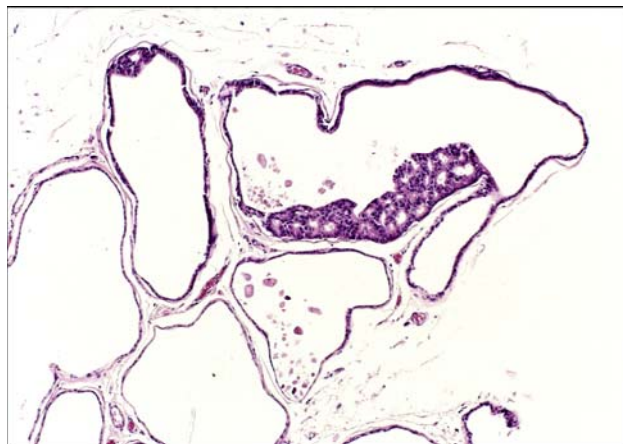


TRAMP

Non-Neoplastic Prostate Lesions

- Inflammation (Fibrosis, Abscesses, Granulomas, Cellular infiltrates, etc.)
 - Rats ~ 3x > Mice
- Hyperplasia
 - Rats = Mice
- Cysts, Acinar dilation, Acinar ectasia

Prostate Hyperplasia



Target Organs for Workshop

- Mammary gland
- Ovary
- Prostate
- Testis

Historical Control Incidences

Interstitial Cell (Leydig Cell) Tumors

TESTIS NEOPLASIA - Inhalation Studies			
----- NIH-07 Diet -----			
Rat (F344)	Adenoma	740/1055	70%
----- NTP-2000 Diet -----			
Rat (F344)	Adenoma	385/499	77%
TESTIS NEOPLASIA - Feed Studies			
----- NIH-07 Diet -----			
Rat (F344)	Adenoma	889/1003	87%
----- NTP-2000 Diet -----			
Rat (F344)	Adenoma	471/510	92%
TESTIS NEOPLASIA - Inhalation Studies			
----- NIH-07 Diet -----			
B6C3F1	Adenoma	7/1070	0.7%
	Hemangioma	1/1070	0.1%

Chemicals Associated with Testis Neoplasia

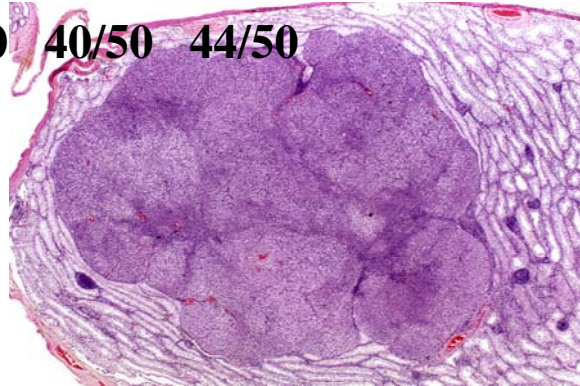
Rat

- Ethylbenzene
- Isoprene

Treatment-Associated Neoplasia (ICT) of Testis in F344 Rats

Ethylbenzene

36/50 33/50 40/50 44/50



Isoprene

33/50 37/50 44/50 48/50

Non-Neoplastic Testis Lesions

- Degeneration
 - Rats > Mice
- Atrophy
 - Rats > Mice
- Interstitial cell hyperplasia
 - Rats 2.5x > Mice
- Inflammation
- Mineralization
 -

In Summary

- Mammary fibroadenomas (~40+%) and testicular interstitial cell tumors (>70%) are common spontaneous neoplasms in F344 rats.
- Mammary gland neoplasia is the most common treatment-associated neoplasm observed in F344 rats, occasionally including transpecies occurrences.
- Treatment-associated ovarian neoplasia has been seen in 10 B6C3F1 mouse cancer bioassays.
- Treatment-associated prostate neoplasia has not been seen in conventional NTP cancer bioassays.
- Treatment-associated testis neoplasia is rare in rats and not seen in mice in NTP cancer bioassays.

Uterus Neoplasia - Rats

UTERUS NEOPLASIA - Inhalation Studies				UTERUS NEOPLASIA - Feed Studies			
----- NIH-07 Diet -----				----- NIH-07 Diet -----			
Rat (F344)	Adenoma	2/1052	0.2%	Rat (F344)	Adenoma	3/1001	0.3%
	Deciduoma	2/1052	0.2%		Carcinoma	4/1001	0.4%
	Granular cell tumor	1/1052	0.1%		Hemangioma	1/1001	0.1%
	Leiomyoma	1/1052	0.1%		Leiomyoma	2/1001	0.2%
	Leiomyosarcoma	2/1052	0.2%		Leiomyosarcoma	2/1001	0.2%
	Stromal polyp	122/1052	11.6%		Stromal polyp	128/1001	12.8%
	Stromal sarcoma	6/1052	0.6%		Stromal sarcoma	5/1001	0.5%
	Schwannoma	3/1052	0.3%		Schwannoma	2/1001	0.2%
----- NTP-2000 Diet -----				----- NTP-2000 Diet -----			
Rat (F344)	Stromal polyp	93/499	18.6%	Rat (F344)	Stromal polyp	90/510	17.6%
	Stromal sarcoma	3/499	0.6%		Stromal sarcoma	2/510	0.4%

Uterus Neoplasia - Mice

UTERUS NEOPLASIA § Inhalation Studies				UTERUS NEOPLASIA § Feed Studies			
----- NIH-07 Diet -----				----- NIH-07 Diet -----			
B6C3F1	Adenoma	3/1077	0.3%	B6C3F1	Adenoma	1/953	0.1%
	Carcinoma	1/1077	0.1%		Carcinoma	4/953	0.4%
	Deciduoma	1/1077	0.1%		Hemangioma	2/953	0.2%
	Granular cell tumor	1/1077	0.1%		Leiomyoma	4/953	0.4%
	Hemangioma	7/1077	0.6%		Leiomyosarcoma	3/953	0.3%
	Leiomyoma	5/1077	0.5%		Stromal polyp	31/953	3.3%
	Leiomyosarcoma	3/1077	0.3%		Stromal sarcoma	4/953	0.4%
	Stromal polyp	39/1077	3.6%				
	Stromal sarcoma	4/1077	0.4%				
----- NTP-2000 Diet -----				----- NTP-2000 Diet -----			
B6C3F1	Carcinoma	5/499	1.1%	B6C3F1	Stromal polyp	13/509	2.8%
	Hemangiosarcoma	3/499	0.6%				
	Stromal polyp	14/449	3.1%				
	Stromal sarcoma	3/449	0.6%				

Chemicals Associated with Uterine Neoplasia

- Rats
 - 3-Amino-9-ethylcarbazole HCl
 - C.I. Direct Blue 15
 - Daminozide
 - 3,3'-Dimethoxybenzidine 2HCl
 - 3,3'-Dimethoxybenzidine - 4,4'-diisocyanate
 - ICRF-159
 - Isophosphamide
 - TCDD (TEF Evaluation)
 - 4,4'-Thiodianiline
- Mice
 - Bromoethane
 - Chloroethane
 - 1,2-Dichloroethane
 - Ethylene oxide
 - Glycidol
 - Procarbazine HCl
 - 1,2,3-Trichloropropane
 - Trimethylphosphate
 - Urethane

Preputial Gland Neoplasia

PREPUTIAL GL NEOPLASIA Š Inhalation Studies				PREPUTIAL GL NEOPLASIA Š Feed Studies			
----- NIH-07 Diet -----							
Rat (F344)	Adenoma	37/1044	3.5%	Rat (F344)	Adenoma	66/998	6.6%
	Carcinoma	48/1044	4.6%		Carcinoma	29/998	2.9%
	Ad or Ca	84/1044	8.0%		Ad or Ca	95/998	9.5%
----- NTP-2000 Diet -----							
Rat (F344)	Adenoma	5/496	1.0%	Rat (F344)	Papilloma	1/998	0.1%
	Carcinoma	9/496	1.8%		Sq. Cell Ca	2/998	0.2%
	Ad or Ca	14/496	2.8%		----- NTP-2000 Diet -----		
				Rat (F344)	Adenoma	23/510	4.5%
					Carcinoma	10/510	1.96%
					Ad or Ca	33/510	6.47%

Chemicals Associated with Preputial Gland Neoplasia

- Rat
 - CI Direct Blue 15
 - 2,4-Diaminoanisole sulfate
 - 3,3'-Dimethoxybenzidine HCl
 - 3,3'-Dimethylbenzidine HCl
 - Isophorone
 - 2-Mercaptobenzothiazole
 - 1,2,3-Trichloropropane
 - Nilidixic Acid
- Mouse
 - Benzene
 - 1,3-Butadiene
 - Dimethylvinyl Chloride
 - Tris(AziridinyI)-phosphine Sulfide