Table 31. Summary of chemicals associated with tunica vaginalis mesotheliomas in rats

Agent	Route	Strain	TVM	LCT	Other treatment-associated tumors
Methyl(acetoxymethyl) nitrosamine	IP	F344	36%	++	NR
Methyl(acetoxymethyl) nitrosamine	IP	SD	15%	+	NR
Methyl(acetoxymethyl) nitrosamine	IP	Buf	46%	0	NR
Ferric saccharate	IP	Wist	47%	NR	NR
Ferric saccharate + NTA	IP	Wist	68%	NR	NR
Cytembena NTP TR 207	IP	F344	74%	++	FR – Mammary fibroadenomas
2,3-Dibromo-1-propanol NTP TR 400	Topic	F344	8%	+	MR&FR – Tumors of the nasal cavity, skin, oral cavity, esophagus, forestomach, intestines, liver, kidneys, Zymbal gland MR – Splenic hemangioma/hemangiosarcoma FR – Clitoral gland tumors MM&FM – Skin & forestomach tumors MM – Liver and lung tumors
Ethylene oxide	Inh	F344	13%	++	MR&FR – Brain tumors FR – Mammary adenomas & adenocarcinomas
1,2-Dibromoethane NTP TR 210	Inh	F344	52%	++	MR&FR – Nasal carcinomas FR – A/B tumors; Mammary fibroadenomas MM – A/B tumors FM – Hemangiosarcomas; S/C Fibrosarcomas & Nasal carcinomas
1,2-Dichloroethane	Inh	F344	10%	NR	MR&FR – S/C fibromas and mammary fibroadenomas FR- Mammary adenomas and adenocarcinomas

Agent	Route	Strain	TVM	LCT	Other treatment-associated tumors
Ethyl telluric NTP Tr 152	Diet	F344	16%	++	MM&FM-Harderian gland tumors
o-NItrotoluene NTP Tox 23; NTP Tox 44 NTP TR 504	Diet	F344	90%	++	MR&FR – S/C tumors & Mammary fibroadenomas MR – Liver tumors (including cholangiocarcinomas) & A/B tumors FR - Liver adenomas MM&FM – Hemangiosarcomas & Cecal carcinomas FM – Liver tumors
o-Toluidine Hydrochloride NTP Tox 44 NTP TR 153	Diet	F344	34%	++	MR&FR-Splenic sarcomas MR – S/C Fibromas FR – U. Bladder carcinoma & Mammary adenomas & adenocarcinomas MM – Hemangiosarcomas FM – Liver adenomas or carcinomas
2,2-bis(bromomethyl)-1,3-propanediol NTP TR 452	Diet	F344	43%	++	MR&FR – Mammary fibroadenomas; oral cavity and esophagus carcinomas; thyroid follicular cell tumors MR – Skin tumors; U. bladder carcinomas; A/B tumors; S/C fibromas; forestomach papillomas; intestinal tumors MM&FM – A/B tumors; Harderian gland tumors MM – Renal adenomas FM – S/C sarcomas
Nitrofurazone NTP TR 337	Diet	F344	14%	+	FR – Mammary fibroadenomas FM – Ovarian tumors
Pentachlorophenol NTP TR 483	Diet	F344	18%	++	MR – Nasal carcinomas MM & FM – Liver & adrenal tumors FM – Hemangiosarcomas
Tartrazine (FD&C Yellow No. 5)	Water	F344	12%	++	FR – Endometrial stromal polyps

Agent	Route	Strain	TVM	LCT	Other treatment-associated tumors
3,3'-Dimethoxybenzidine HCl NTP TR 372	Water	F344	10%	++	MR&FR – Tumors in the oral cavity, large intestine, liver, Zymbal gland and skin MR – Tumors in small intestine and brain FR – Mammary adenocarcinoma; tumors in clitoral gland and uterus
3,3'-Dimethylbenzidine HCl NTP TR 390	Water	F344	7%	+	MR&FR – Tumors of the skin, Zymbal gland, liver, oral cavity, intestines and lung MR – Preputial gland tumors FR – Clitoral gland tumors
Potassium bromate (Multiple published studies)	Water	F344	75%	NR	MR – Kidney and thyroid tumors
Acrylamide (2 published reports)	Water	F344	17%	++	MR&FR – Thyroid follicular tumors FR – Mammary fibroadenomas
Methyleugenol NTP TR 491	Gav	F344	24%	++	MR&FR – Liver tumors; Neuroendocrine stomach tumors MR – Kidney tumors; mammary tumors; S/C tumors MM & FM – Liver tumors MM – Glandular stomach tumors
Benzaldehyde NTP TR 378	Gav	F344	10%	++	MM&FM – Forestomach papillomas
Glycidol NTP TR 374	Gav	F344	83%	++	MR&FR – Brain, forestomach and thyroid tumors MR – Mammary fibroadenomas, Intestinal tumors, skin tumors; Zymbal gland tumors FR – Oral cavity tumors, clitoral gland tumors, leukemia MM&FM – Harderian gland and skin tumors MM – Forestomach, liver and lung tumors FM – Mammary tumors, Uterine tumors, S/C tumors

TVM = highest % incidence tunica vaginalis mesothelioma LCT = Leydig cell tumor response [+ = < 79%; ++ = ≥80%]
MR = Male Rat FR = Female Rat MM = Male Mouse FM = Female Mouse NR = Not reported
SD = Sprague-Dawley Buf = Buffalo Wist = Wistar NTA = Nitrilotriacetate acid
IP = intraperitoneal Tpoic = topical Inh = inhalation Diet = dietary Water = drinking water Gav = gavage

Table 31. Human relevance framework for tunica vaginalis mesothelioma induction in F344 rats secondary to enhanced mesothelial mitogenesis

Alternative Key Events	Degree of Certainty in F344 Rat	Human Relevance
Presence of Leydig cell tumors causally related to tunica vaginalis mesotheliomas	Reasonably certain. Size of Leydig cell tumors correlated with tunica vaginalis mesotheliomas and localized growth factors. Localized peritesticular hormonal imbalance stimulates mitogenic autocrine growth factors from mesothelial cells. (Turek & Desjardins 1979; Gerwin et al., 1987; Karpe et al., 1982; Bartke et al., 1985; Versnel et al., 1988)	Not relevant. Leydig cell tumors are extremely rare in humans. There are significant differences in production and responsiveness between rat and human mesothelial cells. (Clegg et al., 1997; Walker et al., 1995; Walker et al., 1992)
Physical pressure or shearing forces due to enlarged Leydig cell tumor-bearing testes	Good evidence. Evidence for altered growth factor expression in transformed mesothelial cells in vitro. (Tanigawa et al., 1987; Gabrielson et al., 1988; Gerwin et al., 1987; Waters et al., 1997)	Not relevant. Leydig cell tumors are extremely rare in humans. (Clegg et al., 1997; Walker et al., 1995; Walker et al., 1992)
Age-associated increased prolactin leading to decreased circulating testosterone	Certain. Increased prolactin causes decreased LHRH and LH and inhibition of testosterone production. (Mahoney & Hodgen 1995; Capen et al., 2002)	Not relevant. Human Leydig cells do not have LHRH receptors. LH receptors not responsive to prolactin. (Prentice & Meikle 1995)
Decreased prolactin secretion from pituitary via dopamine agonists	Certain for specific chemicals. Serum prolactin levels decrease in rats. Decrease in LH receptors. (Prentice et al., 1992; Prentice & Meikle 1995; Friedman et al., 1999; Uphouse et al., 1982)	Not relevant. Human LH receptors not responsive to prolactin. (Wahlstrom et al., 1983)
Spontaneous age-associated decrease in testosterone and LH receptors and compensatory increase in LH	Certain. Responsible for the high spontaneous incidence of Leydig cell tumors in older F344 rats. (Amador et al., 1985; Maekawa & Hayashi 1992; Takaki et al., 1989; Solleveld et al., 1984; Foster 2007; Tanigawa et al., 1987; Turek & Desjardins 1979; Prentice & Meikle 1995; Capen 1996)	Uncertain. The number of LH receptors is 14 times greater in rats compared to humans. (Prentice and Meikle, 1995)
LHRH receptor agonist induced Leydig cell tumors	Reasonably certain for specific chemicals. Binding to rat LHRH receptors on Leydig cells produces Leydig cell tumors.(Prentice & Meikle 1995)	Not relevant. Human Leydig cells do not have LHRH receptors. (Prentice & Meikle 1995)