

Supplemental Table 1 References. Non-hormonal Chemicals that Induce Potential Sterilizing Effects in Male Animals

Target Organ	Admin ¹	Chemical	Trade Name ³	Species	Dosage	Original Use	Short-term Pathology	Long-term Pathology	Mechanisms of action	T Decreased ¹	Inflammation	Side-Effects	Refs ⁶
Testis	Oral, s.c.	Ketoconazole	Nizoral	Mouse, Rat, Dog, Monkey	10-300 mg/kg	Imidazole antifungal drug	Germ cell apoptosis	Decrease testis wt; germ cell loss; testicular atrophy; azoospermia	Inhibition of cytochrome p450 enzymes, blocking steroidogenesis; reduces testosterone	Yes	Yes	Inhibits steroid synthesis; central nervous system toxicity; adrenal insufficiency	1
		Embelin	N/A	Dog, Rat, Mouse	20-80 mg/kg	Anti-cancer	Reversible infertility; decrease T	Spermatogenesis arrest; decrease testis wt	Inhibition of energy metabolism and sperm motility	Yes	No	None	2
		Dibromochloro-propane	N/A	Rat	50 mg/kg	Nematicide	Multinucleated giant cells; sperm granuloma	Azoospermia	Inhibit sperm glucose metabolism	No	No	Damage to liver, kidneys, stomach	3
		4-Vinylcyclo-hexene diepoxide	N/A	Rat	100-500 mg/kg	Industrial chemical	Decrease sperm count; decrease T	Testis necrosis	Induces oxidative stress	Yes	Yes	Liver, kidney, stomach and brain toxicity	4
		20,25-diazacholesterol dihydrochloride	DiazaCon™	Rat, Mouse, Bird, Squirrel	8-100 mg/kg	Lower serum cholesterol	Decrease T; germ cell loss; multinucleated giant cells	Leydig cell degeneration; testis atrophy	Inhibits steroidogenesis	Yes	No	Inhibits synthesis of glucocorticoids	5
		Quinestrol and Levonorgestrel	EP-1	Rat, wild rodent	0.33-0.67 mg/kg	Female contraceptive; synthetic hormones	Decreased epididymal weight; decreased cauda sperm number; germ cell loss	Testis recovers	Inhibits HPG axis	No	Not determined	Increased weight adrenal gland	6
Testicular and epididymis	Oral, s.c.	Methyl 1-(butylcarbamoyl)-2-benzimidazole-carbamate	Benomyl (Benlate) Carbendazim	Rat	25-500 mg/kg	Fungicides	Increase testis wt; sloughing germ cells; inhibit mitosis; occlusion of efferent ducts	Testis atrophy; decrease testis wt; fibrosis of efferent ducts; azoospermia	Inhibits microtubule polymerization; occlusion of efferent ducts	No	Yes	Hepatotoxicity; genotoxicity; fetal malformations	7
		Lonidamine derivatives	Gamendazole Adjudin	Rat, Mouse, Monkey, Dog, Rabbit	25-100 mg/kg	Anti-cancer	Sloughing germ cells	Testis atrophy; azoospermia	Disruption of Sertoli cell junctions; occlusion of efferent ducts;	No	Yes	Reduced motor activity, palprebral ptosis, lacrimation, tremors and dyspnea	8
Epididymis	Oral, s.c.	3-Chloro-1,2-propanediol	α-Chlorohydrin Epibloc®	Rat, Mouse, Hamster, Dog, Guinea-pig, Sheep, Boar, Monkey	10-140 mg/kg	Organic chemical food contaminant	Immobilization of sperm	Testis atrophy; necrosis; azoospermia	Occlusion of efferent ducts; formation spermatocetes; inhibits epididymal function; inhibits glycolysis	No	Yes	High doses are neurotoxic and nephrotoxic	9
Testis	Intra-testicular ⁴	Zinc compounds	Kastrin, Neutersol™, Zeuterin™, EsterilSol™, Testoblock®, Infertile®	Rat, Dog, Cat, Monkey, Bear, Pig	2.6-58 mg/ml	Dietary supplement; treatment of common cold	Multinucleated giant cells; acute inflammation; edema; testis swelling	Seminiferous tubule necrosis; atrophy;	Sertoli cell barrier damage; massive neutrophilic inflammation; necrosis; tubular fibrosis	Yes	Yes	Scrotal ulceration and dermatitis; necrotizing reactions	10
		4-allyl-2-methoxyphenol	Eugenol Clove oil	Dog	1 ml	Cosmetics; anti-anthelmintic; expectorant	Testis swelling	Seminiferous tubular fibrosis	Testicular necrosis; inflammation	Yes	Yes	Epididymal vacuolation	11

		CaCl ₂ +/- ethanol & hypertonic NaCl	Calchlorin™, Salts	Rat, Dog, Cat, Bull, Goat, Donkey, Ram, Guinea pig, Buffalo	20-50% in water or ethanol	Inorganic salt; food additive; deicing salt; desiccant	Testis swelling; inflammation	Testicular atrophy	Testicular dehydration; necrosis; coagulative fibrosis	Yes	Yes	Scrotal necrosis if leakage	12
		CdCl ₂	Metallic salt	Rat, Mouse, Dog, Rabbit, Hamster	150 µ/kg	Inorganic salt pigment	Hemorrhage; edema; inflammation	Testicular atrophy	Decreased blood flow; ischemia; oxidative stress	Yes	Yes	Toxic to numerous organs, if given oral	13
		1,2,3-trihydroxypropane	Glycerol	Rat, Dog, Cat, Monkey, Rabbit	10-70%	Food additive; soap; laxative	Seminiferous tubule disruption	Testicular atrophy	Hyperosmotic dehydration	Yes	Yes	None	14
		Lactic acid	Chem-Cast®	Rat, Dog, Bull	85-92%	Organic synthesis; food additive	Germ cell degeneration	Testicular atrophy	Sclerosing, caustic chemical; necrosis; fibrosis	Yes	Yes	Scrotal necrosis if leakage	15
		KMnO ₄	N/A	Pig	0.25 g/17 ml acetic acid	Inorganic oxidizing agent; water treatment	N/A	Seminiferous tubular atrophy; fibrosis efferent ducts	Sclerosing, caustic chemical	N/A	Yes	Leydig cell hypertrophy	16
		Metallic & rare earth salts	N/A	Rat, Mouse, Monkey	0.02-0.08 mM/kg	Salts	Focal necrosis	Testicular total necrosis for some salts	Cytolysis, ischemia, necrosis	N/A	Yes	Some Leydig cell loss; early effects on vas deferens sperm; some salts showed no effect	17
		Ethanol	Alcohol	Bull	100%; 10 ml	Organic solvent	Testis swelling; necrosis	Testicular atrophy	Necrosis; inflammation; edema; fibrosis	Yes	Yes	Only 50% became infertile	18
	Intra-Testicular; s.c or i.m	Inflammatory induction agents ⁵	N/A	Guinea pig, Monkey, Rat, Rabbit; Dog; Ram	N/A	Antibody stimulating	Inflammation; seminiferous tubular dilation; testis swelling	Granuloma; necrosis; testicular atrophy	Inflammation;	No	Yes	Injection outside testis required for azoospermia for some agents	19
Epididymis Vas deferens	Intra-lumen	Sclerosing agents ²	N/A	Ram, Goat, Dog, Cat, Rat, Mouse, Monkey	Wide range	Numerous chemicals	Inflammation; epididymis swollen	Granulomas and cysts; tissue scarring; azoospermia	Spermatic granuloma; fibrosis; blockage	No	Yes	Adhesions between epididymis and tunica vaginalis; sometimes testicular effects	20
	Intra-lumen plugs	Silicone, polyurethane elastomers, hydrogels, co-polymers	RISUG® ADAM™ Vasalge®	Rat, Rabbit, Monkey, Man	N/A	Elastomers; gels	Occlusion of vas deferens	Azoospermia; testis and epididymal pathology	Prevention of sperm transport; blockage	No	Yes	Testis focal degeneration; hematoma	21

¹ Administration of the chemical/drug; oral, subcutaneous or cutaneous (s.c.), intramuscular (i.m.), intra-peritoneal or intra-organ (intra-testicular, intra-epididymal, intra-vas deferens); T, testosterone

² Sclerosing agents consist of a broad range of caustic chemicals that induce tissue damage and elicit fibrosis: Quinacrine dihydrochloride, zinc arginate, sodium tetradecyl sulfate, potassium permanganate, ethanol +/- ascorbic acid, silver nitrate, formaldehyde, styrene maleic anhydride, chlorhexidine digluconate, lactic acid, methylcyanoacrylate, urea and ethanol, formaldehyde and ethanol, CaCl₂ in ethanol

³ N/A, not applicable

⁴ Some of these are considered to be sclerosing agents and have been tested as intra-epididymal sterilants.

⁵ Testicular antigens +/- killed bacteria; killed mycobacteria; Freund's complete adjuvant injected into foot after intratesticular injection of turpentine; Freund's complete adjuvant plus testis homogenate

⁶ Supplemental References

1: [Ketoconazole](#) [1-18]

2: [Embelin](#) [19-25]

3: [Dibromochloropropane](#) [26-33]

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