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ToxPath Inc

Tumor Mode of Action

and

Pathogenesis

Pattern of Organ Involvement

- **Suggests a hormonal MOA.**
- **Thyroid, mammary gland & tunica vaginalis testes mesotheliomas.**
- **No increase in organs that one would expect with a genotoxic MOA, e.g., liver, kidney, lymphoid, etc.**

Benign versus Malignant

- **The increase is only in benign tumors.**
- **One would expect an increase in malignant tumors with a genotoxic MOA.**

Mesotheliomas of the tunica vaginalis testes

- **Nothing unique about the mesothelium lining in the testes.**
- **Micro-environment in the presence of Leydig cell tumors.**
- **Physical trauma (irritation) due to enlarged testes from Leydig cells.**

TVM Incidence in Johnson *et al* (1986) & Friedman *et al* (1995)						
Sex	Study	Treatment Dose (mg/kg)				
		0	0.01	0.1	0.5	2.0
Male	Johnson	3/60	0/60	7/60	11*/60	10*/60
	Friedman	8/204	Ń	9/204	8/102	13*/75

Mammary Tumor Incidence in Johnson *et al* (1986) & Friedman *et al* (1995)								
Sex	Tumor	Treatment Dose (mg/kg)						
		0	0.01	0.1	0.5	1.0	2.0	3.0
Female	Fibro-adenoma	10/58 9/96	11/58	9/59	19/58	20*/94	23*/60	26*/100
	Adeno-carcinoma	2/60 2/100	1/60	1/60	2/58	2/100	6/61	4/100

Thyroid Tumor Incidence in Johnson *et al* (1986) & Friedman *et al* (1995)								
Sex	Tumor	Treatment Dose (mg/kg)						
		0	0.01	0.1	0.5	1.0	2.0	3.0
Male	Follicular Cell Adenoma	1/60 3/202	0/58	2/59 9/203	1/59 5/101	Ń	7*/59 15*/75	Ń
	Follicular Cell Carcinoma	0/60 3/202	0/60	0/60 3/203	0/60 0/101	Ń	0/60 3/75	Ń
	Total Tumor Bearing Animals	1/60 6/202	0/60	2/60 12/203	1/60 5/101	Ń	7*/60 17/75	Ń
Female	Follicular Cell Adenoma	0/58 0/100	0/59	1/59	1/58	7/100	3/60	16/100
	Follicular Cell Carcinoma	1/58 2/100	0/59	0/59	0/58	3/100	3/60	7/100
	Total Tumor Bearing Animals	1/58 2/100	0/59	1/59	1/58	10/100	5*/60	23*/100

Incidence of Gliosis & Malignant Reticulosis in Johnson *et al* (1986)

Sex	Tumor type	Treatment Dose (mg/kg)				
		0	0.01	0.1	0.5	2.0
Male	Gliomas Š Brain	3/60	2/60	0/60	3/60	4/60
	Gliomas Š Spinal Cord	2/60	0/60	0/60	0/60	4/60
	Tumors of Glial Origin	5/60	2/60	0/60	3/60	8/60
	Malignant Reticulosis	0/60	0/60	0/60	0/60	0/60
Female	Gliomas Š Brain	0/60	2/60	1/60	1/60	7/60
	Gliomas Š Spinal Cord	1/60	0/60	0/60	0/60	3/60
	Tumors of Glial Origin	1/60	2/60	1/60	1/60	9*/60
	Malignant Reticulosis	0/60	0/60	0/60	0/60	0/60

Incidence of Gliosis & Malignant Reticulosis in Friedman *et al* (1995)

Sex	Tumor type	Treatment Dose (mg/kg)			
		0	0.1	0.5	2.0
Male	Gliomas Š Brain	2/204	1/98	1/50	2/75
	Gliomas Š Spinal Cord	0/172	1/68	0/37	1/51
	Tumors of Glial Origin	2/204	2/98	1/50	3/75
	Malignant Reticulosis	1/204	1/98	0/50	0/75

		0	1.0	3.0
Female	Gliomas Š Brain	0/100	2/100	2/100
	Gliomas Š Spinal Cord	0/99	0/20	1/90
	Tumors of Glial Origin	0/100	2/100	3/100
	Malignant Reticulosis	0/100	2/100	3/100