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The response of the Tg.rasH2 mouse test system to two known carcinogens (urethane and MNU – N-methyl-N-nitrosourea)

Animals of Group 1 (15 males and 15 females) received purified water by oral gavage once daily for 26 consecutive weeks. Animals of Group 2 (15 males and 15 females) received a total of 3 intraperitoneal injections of Urethane (1000 mg/kg each) at 2-day intervals (i.e., on Day 1, 3 and 5). Animals of Group 3 (15 males and 15 females) received a single intraperitoneal injection of MNU (75 mg/kg). The dose volume was 10 mL/kg for all animals.

MICROSCOPIC FINDINGS: PROLIFERATIVE LESIONS

Test article	Control		Urethane		MNU	
	Males	Females	Males	Females	Males	Females
Lungs:						
Adenoma, bronchiolo-alveolar	0	0	15	15	2	2
Carcinoma, bronchiolo-alveolar	0	2	7	13	1	0
Harderian Glands:						
Adenoma, acinar cell	1	0	7	6	0	4
Adenocarcinoma	0	0	2	1	0	0
Blood vessel:						
Hemangioma	0	0	0	1	0	1
Hemangiosarcoma	1	1	15	13	2	3
Hemolymphoreticular (all sites):						
Lymphoma, malignant	1	0	0	1	9	9
Skin & Subcutis (including ear):						
Papilloma, squamous cell	0	0	0	0	6	9
Fibrosarcoma	0	0	0	0	1	0
Tumor, basal cell, malignant	0	0	0	1	0	0
Stomach (non-glandular):						
Papilloma, squamous cell	0	0	0	0	6	9
Carcinoma, squamous cell	0	0	0	1	1	0
Uterus:						
Polyp, endometrial stromal	NA	0	NA	0	NA	1
Polyp, glandular	NA	0	NA	0	NA	4
Vagina:						
Fibroma	NA	0	NA	0	NA	2
Papilloma, squamous cell	NA	0	NA	0	NA	1

NA = Not Applicable

Hemangiosarcoma (spleen [Figure 1], lungs, ileum, liver, uterus and/or vagina) and bronchiolo-alveolar adenoma [Figure 2] and/or adenocarcinoma [Figure 3] of the lungs were observed in the majority of the Group 2 (Urethane-treated) animals and were considered to be main cause of mortality/morbidity of these animals. Hemangiosarcoma affected 28/30 animals, while bronchiolo-alveolar adenoma/adenocarcinoma of the lungs was observed in 20/30 Group 2 mice. Acinar cell adenoma of the Harderian glands (13/30) and adenocarcinoma of the Harderian glands (3/30; [Figure 4]) were considered to be third most frequent tumor observed in the mice receiving Urethane.

Malignant lymphoma (multiple organ distribution; kidneys [Figure 5]) was found in 18/30 Group 3 (MNU) mice and was considered to be the cause of demise for 17/23 animals. Hemangiocarcinoma was considered to be the second most frequent tumor affecting 5/30 mice.

MICROSCOPIC FINDINGS: NON-PROLIFERATIVE LESIONS

A high incidence of subcapsular hyperplasia of the adrenals was observed in 22/30 Group 1, 17/30 Group 2 and 18/29 Group 3 mice. Similarly, a high incidence of glandular hyperplasia of the uterus [Figure 6] was noted in 13/15 Group 1, 10/15 Group 2 and 13/15 Group 3 mice. These findings were considered to be common background findings of the Tg.rasH2 mouse.

Retinal atrophy of the eyes [Figure 7] was observed in 24/30 Group 3 mice and was considered to be MNU-related toxicological effect.

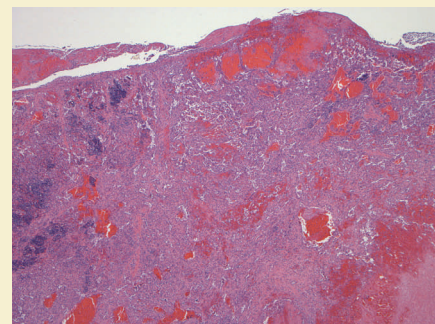


Figure 1

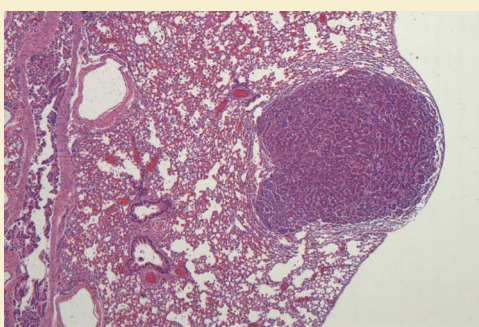


Figure 2

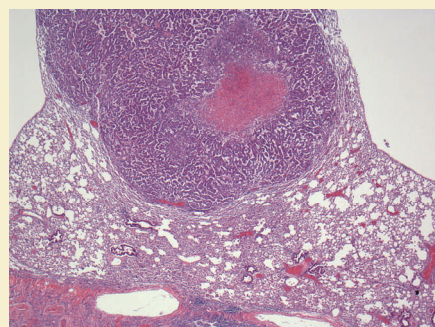


Figure 3

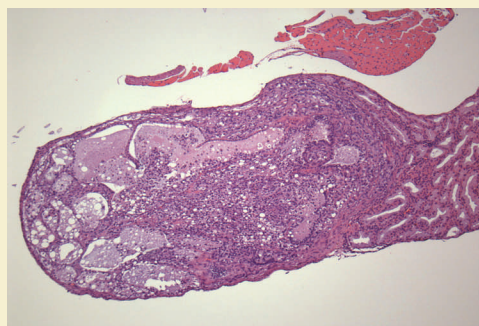


Figure 4

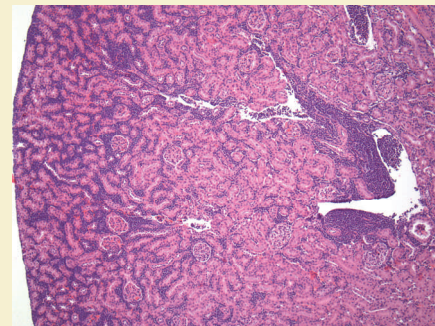


Figure 5



Figure 6

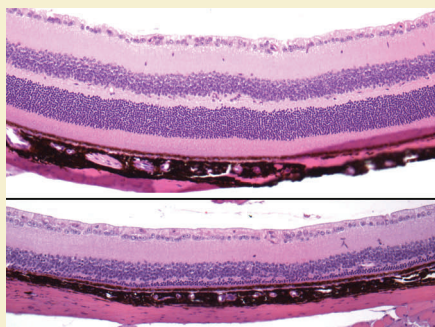


Figure 7