The incidence of lung and spleen tumors in positive control group of Tg.rasH2 mice sourced from CLEA, Japan

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INTRODUCTION

The 6-month carcinogenicity study in Tg.rasH2 mice is a valid alternative to traditional 2-year bioassays in mice. Currently these mice are available from two breeder sources, viz. Taconic, USA and CLEA, Japan.

For mice sourced from CLEA, there is a dearth of published data on **positive control urethane.**

Urethane, at 1000 mg/kg bwt has been unduly toxic to mice, but not at 500 mg/kg[1,2].

METHOD

We conducted a study in Tg.rasH2 mice sourced from CLEA, Japan, to generate positive control data for urethane administered at a lower dose of 500 mg/kg bwt on days 1, 3 and 5.

- in 10 male & 10 female mice
- intraperitoneal injections,
- sacrificed at 13 weeks after the first dose.

Observations:

- Gross necropsy.
- Lungs and spleen examined microscopically, and the tumors identified.

Comparison with Published Data

Made with published[1,2] tumor incidence in lungs and spleen, from 60 mice, sourced from Taconic and treated with urethane at 500 mg/kg bwt on days 1, 3 & 5.

The present study demonstrated comparability of carcinogenic potential of positive control urethane in Tg.rasH2 mice sourced from two breeding facilities - Taconic and CLEA.

Figure 1

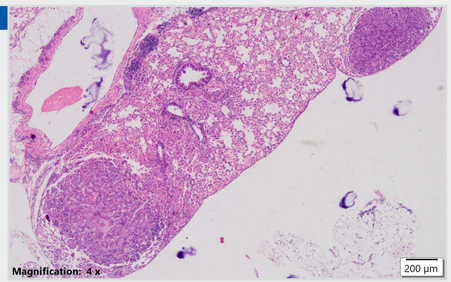


Figure 2

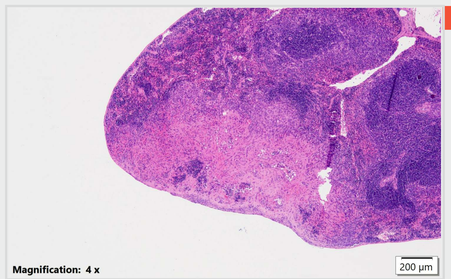


Figure 3

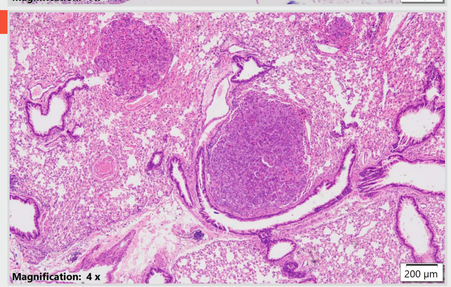
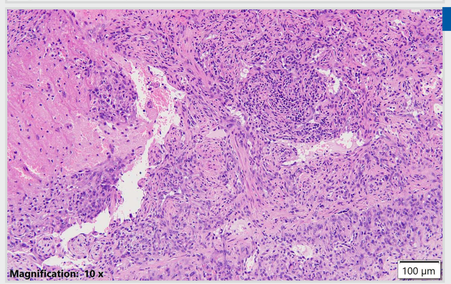


Figure 4



References:

1. Paranjpe, Madhav et al. Proposal to Eliminate Urethane-Treated Positive Control Dose Groups in 26-Week Tg.rasH2 Carcinogenicity Studies. International Journal of Toxicology. 2021 Vol. 40 (3).

2. Jeffrey L. Ambroso et al. Assessment of the Carcinogenic Potential of Pretomanid in Transgenic Tg.rasH2 Mice, International Journal of Toxicology 2022, Vol. 41(5) 367–379

Conflict of interest disclosure:

- MP is a Consultant and Director of Pathology at Intox Pvt Ltd.
- AK, ND, GJ, CM, PN, SP and AV are in the employment of Intox.
- Intox is a subsidiary of Aragen Life Sciences.

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RESULTS

No remarkable toxicity observed at 500 mg/kg of urethane injected IP.

Tumor Incidence:

Lungs - Alveolar bronchiolar adenomas/adenocarcinomas in all the 20/20 mice (100% incidence) (Fig. 1 & 3); Hemangiosarcomas co-existing in 3/20 mice

Spleen - Hemangiosarcomas in all the 20/20 mice (100% incidence) (Fig. 2 & 4).

Table 1 - Incidence of Lung and Spleen Tumors in Tg.rasH2 Mice given Intraperitoneal Injections of Urethane at 500 mg/kg bwt on Days 1, 3 and 5 and Terminated after 13 Weeks

Source of Data	Published Studies (1, 2)	Present Study at Intox
Incidence based on	60 Mice	20 Mice
Tumor Types	**% Incidence**	
Pulmonary adenoma/adenocarcinoma	100	100
Splenic hemangiosarcoma	70	100

DISCUSSION & CONCLUSIONS

The comparison with published data in Taconic sourced Tg.rasH2 mice reveals that,

- Pulmonary adenomas/adenocarcinomas - incidence was fully comparable
- Splenic hemangiosarcomas - incidence was slightly higher despite a lower dose of urethane.
- There were no overt clinical signs of toxicity due to the lowered dose of urethane.