ToxWorks

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Evaluation of the Ramazzini Foundation Study of Methanol in Rats

A Comparison of Diagnoses by the RF Study Pathologist and a Recent NTP Review Team

Comparison summarized by
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Methanol Institute

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In 1990, The Ramazzini Foundation (RF) initiated a carcinogenicity study of methanol in rats. The RF reported increased lympho-immunoblastic lymphoma (LIL) primarily in the lungs and ear carcinomas of rats exposed to methanol (Soffritti et al., 2002). Soffritti et al. reported a significant increase in rats with any type of leukemia, lymphoma, or histiocytic sarcoma in the high-dose males compared to the controls (38/100 vs. 24/100). Several articles have questioned whether this truly represented a lymphoma or a respiratory infection (Cruzan, 2009, Schoeb et al., 2009, 2010). In April 2010, a team of three pathologists from the National Toxicology Program (NTP) reviewed the histologic sections of lung, liver, spleen, lymph nodes, thymus, ear canal, Zymbal's gland, and cranium from high dose (n=100) and control (n=100) male SD rats in the methyl alcohol study. They jointly reviewed slides from 10 animals in each group and then each reviewed 30 additional animals from the control and high-dose groups. Thus the slides from each animal in the control and high-dose male groups were examined by at least one NTP pathologist. A report (Malarky et al., 2010) stated "In general, the NTP pathologists diagnosed fewer neoplasms and more inflammatory lesions in the rats from the methyl alcohol study." However, the report did not provide any quantitative details of the NTP review. Through a Freedom of Information Act (FOIA) request the Methanol Institute obtained a copy of the Slide Review Worksheet comparing individual slide diagnoses by RF and NTP (identified as c00117-68 srws.pdf).

I have examined the Slide Review Worksheets and the results can be summarized as follows:

The NTP pathologists did not agree with the RF pathologist on most lymphomas and ear cancers.

1. RF reported 23 rats with LIL present only in the lungs; the NTP pathologists concluded that only one of these lesions represented a lymphoma.

2. RF reported an additional 29 rats with LIL present in the lungs and other tissues; NTP concluded that only 12 of these represented lymphomas.

3. The RF reported 33 rats with carcinomas in the ear; NTP concluded that only 15 of these represented carcinomas.

The NTP analysis of the RF slides does not support a conclusion of increased cancers from methanol exposure. According to NTP, no rats in the control group and only 1 rat in the high-dose (20,000 ppm) group had lymphoma present only in the lung. According to the NTP pathologists, 5/100 control rats had lymphoma in lungs plus other organs and 6/100 in high-dose rats. The total number of control rats with leukemias, lymphomas or histiocytic sarcomas in the lung and other tissues was 13/100 vs. 9/100 in the high-dose rats. Ear carcinomas were reported by the NTP pathologists in 6/100 controls and 9/100 high-dose rats. None of the incidences in the high-dose males were significantly different from the controls ($p>0.05$ by Fisher's exact test). Therefore, none of the cancers that the RF publication reported as increased was reported as increased by NTP.

Treatment	Incidence by RF	Incidence by NTP
LIL lung only		
Control	10	0
High-Dose	13	1
LIL in lung plus others		
Control	16	5
High-Dose	36	6
Total rats with any LHR		
Control	24	13
High-Dose	38	9
Ear Carcinomas		
Control	9	6
High-Dose	24	9

LIL = lympho-immunoblastic lymphoma; NTP referred only to lymphomas of any type without using the term LIL
LHR = tumors of the lymphohematopoieticreticular system (i.e, leukemias, lymphomas, histocytic sacromas)

References

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Appendix. Individual Animal Findings for Lung

Control				High-Dose (20,000 ppm)		
An #	RF	NTP		An #	RF	NTP
Lung only lymphoma						
704	LIL	No		115	LIL	No
707	LIL	Lym-lu+ly		126	LIL	No
736	LIL	No		143	LIL	No
751	LIL	No		148	LIL	No
753	LIL	No		149	LIL - lu+	Lym lu only
755	LIL	No		158	LIL	No
757	LIL	No		162	LIL	No
774	LIL	No		163	LIL	No
791	LIL	No		180	LIL	No
797	LIL	No		188	LIL	No
				191	LIL	No
				192	LIL	No
				196	LIL	No
				198	LIL	No
Total lung only	10	0			13	1
Lymphoma in lung and other tissues						
707	Lu only	lu + ly		106	LIL	No
708	LIL	No		111	LIL	lym
714	LIL	lym		112	LIL	lym
715	Leukemia	lym		119	LIL	lym
726	LIL	lym		142	LIL	No
737	LIL	No		145	LIL	No
741	LIL	No		149	LIL	Lym lu only
794	LIL	lym		151	LIL	lym
				156	LIL	No
				157	LIL	No
				161	LIL	No
				165	LIL	No
				167	LIL	No
				169	LIL	No
				175	LIL	No
				178	LIL	No
				179	LIL	No
				181	LIL	lym
				183	LIL	lym
				185	LIL	No
				186	LIL	No
				190	LIL	No
				199	LIL	No
Total lung + other	6	5			23	6