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~ October 2012 ~

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Item ID Number	03099	☐ **Not Scanned**
Author		
Corporate Author	Industry Task Force on 2, 4-D Research Data	
Report/Article Title	Typescript: Summary of Combined Toxicity and Oncogenicity Study in Rats with 2, 4-D	
Journal/Book Title		
Year	0000	
Month/Day		
Color	☐	
Number of Images	4	
Description Notes		

INDUSTRY TASK FORCE ON 2,4-D RESEARCH DATA

SUMMARY OF COMBINED TOXICITY AND ONCOGENICITY STUDY IN RATS WITH 2,4-D

By 2,4-D Task Force

On June 2, 1986 the 2,4-D Task Force submitted to the Environmental Protection Agency a two year rat study conducted by Hazleton Laboratories (Vienna, Virginia). The study was designed to evaluate the chronic toxicity and oncogenicity of 2,4-D when fed daily to rats. The treated rats received 2,4-D at levels of 1, 5, 15, and 45 mg/kg/day. A concurrent control group received only the basal diet. Criteria evaluated for signs of compound effect included survival, clinical observations, body weights, food consumption, clinical pathology, organ weights, gross pathology and histopathology.

No compound-related effects on survival, clinical observations, or gross pathology were noted. Also, no definitive clinical pathology changes were noted. During the study body weight and food consumption values in the 45 mg/kg/day males and females were slightly decreased when compared to the control values. Treatment-related increases in absolute and relative kidney weight were observed in the high dose groups of both sexes. These effects were supported by the finding of microscopic alterations in the kidneys of both sexes at all dose levels except at 1 mg/kg/day. The overall "no-observed-effect-level" was determined to be 1 mg/kg/day.

A thorough microscopic examination of an extensive number of organs generally revealed a normal range of non-tumor and tumor observations. A statistically significant higher number of astrocytomas (brain tumors) was found in the brains of the 45 mg/kg/day male rats. No comparable increase, however, was observed in the 45 mg/kg/day female rats or in any of the males and females treated at lower levels. The observed incidence of astrocytomas is set forth below:

Incidence of Astrocytomas

	Male	Female
Control	1/60	0/60
1 mg/kg	0/60	1/60
5 mg/kg	0/60	2/60
15 mg/kg	2/58	1/60
45 mg/kg	6/60*/	1/60

While the incidence of astrocytomas in the male rats at the 45 mg/kg/day level was statistically significant, neoplasms (tumors) often occur spontaneously in various organs of rodents in a random distribution among test groups in any study. This random distribution may produce a statistically significant increased incidence either in the control or one of the treatment groups; therefore, statistical analysis alone may not be meaningful in assessing the carcinogenic potential of a test substance. A careful biological analysis must be made in order to distinguish between spontaneous and compound-induced tumors.

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*/ It should be noted that the Laboratory diagnosed 6 astrocytomas out of 60 animals in this group. A third party reviewer, however, did not consider one of the lesions to be an astrocytoma. The tumor incidence he observed for this group was 5/60.

To this end, the Task Force commissioned an extensive third party review of the observed brain tumors. This review concluded that the tumors in the 2,4-D study did not conform to published biological characteristics of chemically-induced brain tumors (Koestner, 1986). The characteristic features for known neurocarcinogens are:

Increased incidence beyond expected control levels

Shift of tumor appearance to a younger age (decreased survival time)

Demonstration of dose-effect relationship

Trend toward anaplasia

Presence of preneoplastic lesions

Multiplicity of tumors in individual animals

Tumor occurrence in both sexes

Tumor occurrence also in peripheral nervous system

Tumor induction outside the nervous system

Genotoxicity, mutagenicity, chromosomal aberrations

None of these criteria were met in the 2,4-D study. Therefore, the uneven distribution of the tumors, clustering within the high dose group, is most likely by chance and is attributed to biological variation.

In conclusion, it is the opinion of the 2,4-D Task Force that the two year rat study confirms the safety of 2,4-D for the biological parameters the study was designed to evaluate and that the herbicide is not a neurocarcinogen.

REFERENCES

Koestner, A., The Brain-Tumour Issue in Long-Term Toxicity Studies In Rats. Fd. Chem. Toxic. 24:139-143, 1986.