UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: **TRICHLORFON**: Revised Tumor Analysis of Mouse Carcinogenicity Study for Consideration by the HED Cancer Assessment Review Committee

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Executive Secretary
Cancer Assessment Review Committee
Health Effects Division (7509C)

Registrant:	Bayer Corporation Agricultural Division
Chemical:	dimethyl (2,2,2-trichloro-1-hydroxyethyl) phosphonate
Synonym:	Trichlorfon
Caswell No.	385
P.C. Code:	057901
MRID:	44627701

A revised statistical analysis of the tumor data from the CD-1 mouse carcinogenicity study on **Trichlorfon** was submitted recently, and the results indicate that there is a significant increase in the incidence of mammary gland tumors in the female mice at the high-dose level compared to the control incidence. The Cancer Assessment Review Committee is requested to consider this revised analysis of the tumor data and determine whether a change in the classification of Trichlorfon with respect to carcinogenic potential is warranted.

The Health Effects Division Carcinogenicity Peer Review Committee [CPRC] previously evaluated Trichlorfon [April 6, 1994 and August 31, 1994], and it was concluded that the tumors associated with the administration of Trichlorfon to F334 rats [lung and kidney tumors] occurred only at doses that were determined to be excessively toxic [based on cholinesterase inhibition and other clinical

signs of toxicity] to the rats. Based on these findings, the consensus of the CPRC was that these tumors were not considered relevant to a consideration of the potential carcinogenicity of Trichlorfon for humans, and Trichlorfon was classified as a Group E. The previous assessment of the tumor incidence in mice that was presented to the CPRC did not include an evaluation of the incidence of mammary tumors.

In the classification of carcinogenic potential section of the CPRC report, it is stated that some members felt that a Group D classification was more appropriate, based on the following: Although the significant increase in tumors occurred only at an excessive dose in both sexes of rat, the increases were statistically significant by pairwise comparison with controls. Additionally, the incidences were well outside historical controls, there were statistically-significant positive trends, and these tumors of the lung and kidney are uncommon in the rat. It was also noted that the response observed in the lungs of female mice, as well as the pheochromocytomas in male rats, could be considered as equivocal evidence, and that the data from genotoxicity studies and SAR were equivocal also.

Recently, the Registrant submitted additional statistical analyses [MRID 44627701] of survival and tumor incidence by Peto's survival-adjusted trend test methods for the mouse carcinogenicity study [MRIDs 40782401, 40844301, and 41608601], as requested by the Food and Drug Administration [FDA]. The Registrant concludes that the new assessment indicates no statistically-significant differences in mortality rates among the groups [both sexes], and the Peto analysis of tumor data in **males** confirmed the original study analysis demonstrating no statistically increased incidence of neoplasms. Additionally, it is stated that the nonstatistical increase in hepatocellular adenoma in **males** discussed in the original report was confirmed; however, there was no overall combined increase in proliferative hepatocellular lesions.

In **females**, the combined mammary gland epithelial neoplasia and adenocarcinoma/adenoacanthoma were statistically significant according to the modified guidelines proposed by Haseman for rare and common tumors. The Registrant states that, as observed in the original report, none of the incidences of individual mammary epithelial tissue tumors [adenoma, adenocarcinoma, or adenoacanthoma] were significantly increased by Chi-Square and Fisher's Exact tests. The Registrant indicated that the analysis by the Peto test confirmed the original result when the tumors were evaluated individually, but the mammary gland tumors in the high-dose females were statistically significant only when analyzed together [combined], as suggested by McConnell [1986]. The combined incidence of mammary epithelial tumors in female rats is 1, 2, 0, 8 [0 ppm, 300 ppm, 900 ppm, 2700 ppm, respectively].

Table 1. Comparison of Mammary Tumor Incidence [% based on 1/28/99 SAB memo] to Historical Control Data						
	Trichlorfon [ppm]				Laboratory HC	Literature HC
tumor type	0	300	900	2700	N/A	N/A
adenoma	0	1 [3%]	0	2 [6%]		0%-2% [1995]
adenocarcinoma♪	1 [2%]	1 [2%]	0	4 [10%]		0%-12.2% [1995]
adenoacanthoma♪	0	0	0	2 [8%]		0%-4.2% [1995]
combined	1 [2%]	2 [5%]	0	8 [20%]	0%-6% {9/647}	3.8%-12.5% [1988] 0%-12.2% [1995] 2.8% (20/725) [1992]

♪ literature for adenocarcinoma/adenoacanthoma 0%-13.2%, 5/38 mice [1971];

It is stated that the incidence exceeds the testing laboratory historical control incidence for combined mammary epithelial tumors 1.4% [9/647; range 0%-6%] for studies performed from 1975-1995. With respect to the incidences of adenocarcinomas and adenoacanthomas observed in this study, these are said to be within the historical control range reported for matched-aged CD-1 mice. The Registrant concludes that (1) the combined mammary epithelial tumor incidence observed in the Trichlorfon mouse study exceeded the laboratory historical control range but was "close to the range reported in the literature", (2) the incidence of malignant tumors was within the literature historical control range, and (3) there was no associated increase in epithelial hyperplasia or preexisting chronic inflammatory changes in these mice. The registrant's overall conclusion is that the borderline incidence of mammary gland [epithelial] tumors in the high-dose females is an incidental change for the following reasons: (1) Peto analysis was not statistically significant for individual mammary tumors; (2) there was no linear dose-related response as there were no tumors in the mid-dose group; (3) latency for the tumors in the high-dose group was not decreased; (4) there was no associated increase in epithelial hyperplasia or preexisting chronic inflammatory changes in these mice; and (5) the combined mammary epithelial tumor incidence was near the range reported in the literature.

Mammary Tumors

Attached is the Carcinogenicity Peer Review of Trichlorfon [dated 2/28/95] and the assessment of the new statistical evaluation by Science Analysis Branch [SAB memo dated January 28, 1999], which considers **only** mammary tumors in female mice.

Female mice had significant trends for mammary gland adenocarcinomas and combined adenomas, adenocarcinomas and adenoacanthomas, both at $p < 0.01$. There was also a significant trend for mammary gland adenoacanthomas at $p < 0.05$. Female mice showed a significant difference in the pair-wise comparison of the 2700 ppm dose group with the controls for mammary gland combined adenomas, adenocarcinomas and adenoacanthomas at $p < 0.05$.

Table 1. Trichlorfon - Charles River CD-1 Mouse Study
Female Mammary Gland Tumor Rates[+] and
Peto's Prevalence Test Results (p values)

Tumor Type/Dose (ppm)	0	300	900	2700
Adenomas (%) p=	0/36 (0) 0.068	1/39 (3) 0.296	0/29 (0) -	2[a]/32 (6) 0.088
Adenocarcinomas (%) p=	1/42 (2) 0.008**	1/41 (2) -	0/41 (0) -	4[b]/41 (10) 0.121
Adenoacanthomas (%) p=	0/32 (0) 0.010*	0/33 (0) -	0/26 (0) -	2[c]/24 (8) 0.159
Combined (%) p=	1/42 (2) 0.000**	2/41 (5) -	0.41 (0) -	8/41 (20) 0.014*

[+]Number of tumor bearing mice/Number of mice examined, excluding those that died or were sacrificed before observation of the first tumor.
[a]First mammary gland adenoma observed at week 91, 2700 ppm.
[b]First mammary gland adenocarcinoma observed at week 76, 2700 ppm.
[c]First mammary gland adenoacanthoma observed at week 101, 2700 ppm.
Note: Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.