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

AUG 17 1988

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Third Peer Review of Dichlorvos - Reevaluation Following the April 18, 1988 Meeting of the NTP Panel of Experts.

FROM: Judith W. Hauswirth, Ph.D. Judith W. Hauswirth 6/27/88
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TO: George LaRocca
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The Peer Review Committee met on June 2, 1988 to discuss the impact of the April 18, 1988 meeting of the NTP Panel of Experts on the classification of the carcinogenicity of Dichlorvos (DDVP).

A. Individuals in Attendance:

1. Peer Review Committee: (Signatures indicate concurrence with the peer review unless otherwise stated.)

Theodore M. Farber	Theodore M. Farber
William Burnam	Wm J Burnam
Judith W. Hauswirth	Judith W. Hauswirth
Esther Rinde	Esther Rinde
Lynnard Slaughter	L. J. Slaughter
Kerry Dearfield	Kerry Dearfield
Richard Levy	Richard A. Levy
Robert Beliles	Robert Beliles

2. Scientific Reviewers: (Non-committee members responsible for presentation of data; signature indicates technical accuracy of panel report.)

Irving Mauer	Irving Mauer
Bernice Fisher	Bernice Fisher

3. Peer Review Members in Absentia: (Committee members who were unable to attend the discussion; signatures indicate concurrence with the overall conclusions of the Committee.)

Anne Barton

John A. Quest

Reto Engler

Richard Hill

Diane Beal

Marion Copley

4. Scientific Reviewers in Absentia: (Non-committee members whose signature indicates technical accuracy of panel report.)

Joycelyn Stewart

Albin Kocialski

B. Material Reviewed:

The first and second peer review documents on DDVP, the comments of the Scientific Advisory Panel and the transcript of the NTP Panel of Experts meeting of July 14, 1987 were made available to the Committee for review.

C. Considerations:

The relevant points discussed at the April 18, 1988 NTP Panel of Experts meeting were: (1) the incidences of pancreatic acinar cell adenomas after additional sectioning of pancreata from F344 rats from the two-year studies; and (2) effects of DDVP administration on growth of transplantable rat mononuclear cell leukemias in male F344 rats.

1. Results of the Recut of the Pancreas:

Longitudinal sections were cut from the pancreas of male and female rats of all test groups. The results can be found summarized in Appendix 1. There was a positive dose-related trend for total adenomas for male rats. There is no historical control data to compare these results with, since NTP does not routinely do longitudinal sectioning.

2. Effect of DDVP on the Growth of Transplantable Rat Mononuclear Cell Leukemias in Male F344 Rats:

DDVP was positive in this model. There was a strong structure activity relationship for this effect with other dialkyl esters of phosphoric acid.

The NTP scientists concluded from the results discussed under points 1 and 2 above that the increased incidence of mononuclear cell leukemias in DDVP treated rats was treatment-related and from the results of the longitudinal

sectioning of the pancreas that the evidence for oncogenicity in male F344 rats should be down-graded from clear evidence to some evidence of oncogenicity. The downgrading of the level of evidence was based upon both the incidence of mononuclear cell leukemia and of pancreatic acinar cell adenomas. The level of evidence in female rats remained at equivocal. The results of the mouse study were not discussed and therefore, the level of evidence remained at clear for female mice and at some for male mice based upon an increased incidence of stomach papillomas.

The Toxicology Branch Peer Review Committee considered the above information at their meeting and concluded that the classification of DDVP should remain a B_2. They based this conclusion upon the following points:

1. Results of the transplantable rat mononuclear cell leukemia model indicate that the incidence of mononuclear cell leukemia found in DDVP treated F344 rats was treatment-related;

2. Although the results of longitudinal sectioning of the pancreas diminished the significance of the pancreatic acinar adenomas in male rats, the incidence of animals with multiple adenomas was still increased with DDVP treatment.

3. DDVP is a direct acting mutagen and alkylates DNA.

The Committee considered that this is an interim classification since:

1. Mr. S. Jellinek will be submitting the results of a Japanese study on DDVP administered in drinking water to the Agency for review [Since this meeting occurred, this study has been submitted and is under review in Toxicology Branch]; and

2. Several in vivo mutagenicity studies on DDVP which have been reported as positive in the literature are to be reviewed by Toxicology Branch Scientists. These studies are found in the following literature references:

a. Dzwonkowska, A.; Hubner, H. (1986) Induction of chromosomal aberrations in the syrian hamster by insecticides tested in vivo. Arch. Toxicol. 58:152-156.

b. Fischer, G. W.; Schneider, P.; Scheufler, H. (1977) Sur Mutagenitat von dichloroacetaldehyde und 2,2-Dichlor-1,1-dihydroxyathanphosphonsauremethylester, moglichen Metaboliten des phorphoroorganischen Pesticides Trichlorphon. Chem. Biol. Interact. 19:205-213.

c. Gupta, A.K.; Singh, J. (1974) Dichlorvos (DDVP) induced breaks in the salivary gland chromosomes of Drosophila melanogaster. Curr. Sci. 43:661-662.

d. Hanna, P.J.; Dyer, K.P. (1975) Mutagenicity of organophosphorus compounds in bacteria and Drosophila. Mutat. Res. 28:405-420.

e. Krause, W.; Homola, S. (1972) Beeinflussung der Spermiogenese durch DDVP (Dichlorvos). Arch. Dermatol. Forsch. 244:439-441.

f. Wyrobek, A.J.; Bruce, W.R. (1975) Chemical induction of sperm abnormalities in mice. Proc. Natl. Acad. Sci. USA 72:4425-4429.

Appendix I

Results of Longitudinal Sectioning of the Pancreas
of Male and Female Fischer 344 Rats Treated with DDVP

	Control	Dose (mg/kg) 10.0 mg/kg	20.0 mg/kg
Lesion: Pancreas		Males	
hyperplasia	37/50	45/49	39/50
single acinar adenomas	16/50	8/49	14/50
multiple acinar adenomas	9/50	22/49	19/50
total adenomas	25/50	30/49	33/50
		Females	
hyperplasia	21/50	23/47	30/50
single acinar adenomas	2/50	3/47	5/50
multiple acinar adenomas	0/50	0/47	1/50
total adenomas	2/50	3/47	6/50

For comparison the draft NTP report had the following incidences reported for the above pancreatic lesions:

		Males	
hyperplasia	9/50	9/49	9/50
single acinar adenomas	14/50	18/49	17/50
multiple acinar adenomas	2/50	7/49	13/50
total adenomas	16/50	25/49	30/50
		Females	
hyperplasia	2/50	3/47	0/50
single acinar adenomas	1/50	1/47	4/50
multiple acinar adenomas	0/50	0/47	0/50
total adenomas	1/50	1/47	4/50