The CPRC met for a second time on September 29, 1987, to examine the issues raised by the SAP with respect to the classification of the carcinogenicity of dichlorvos (Ref. 5). Upon reconsideration, the Committee concluded that the results of the NTP studies indicate that dichlorvos demonstrates sufficient evidence of carcinogenicity in the male rat and female mouse to confirm the initial classification of dichlorvos as a Group B2 carcinogen.

The committee concluded that "the results of the NTP bioassays indicate that DDVP demonstrates sufficient evidence of carcinogenicity in the male rat and in the female mouse since: (1) A dose-response relationship of statistical significance was seen for pancreatic adenomas (which have the potential to progress towards malignancy) and mononuclear cell leukemia in male rats, (2) a doseresponse relationship of statistical significance was seen in the female mouse for forestomach squamous cell papillomas which have the potential to progress to carcinomas, (3) the presence of some forestomach carcinomas (which are rare) was seen in the female mouse, (4) a significant positive trend was seen for forestomach papillomas in male mice at a dose that did not achieve an MTD, (5) supporting evidence provided by a statistically significant increase in mammary tumors at the low dose in the female rat which was associated with a significant trend, and (6) mutagenicity data was available indicating that DDVP is positive for mutagenicity in vitro in bacterial and mammalian cells both with and without metabolic activation. The Committee, thereby, confirmed their initial classification of DDVP as a B2 oncogen.

The CPRC had a third meeting on June 2, 1988, to review the conclusions of an April 1988 meeting of NTP Panel of Experts on the carcinogenic classification of dichlorvos (Ref. 6). Scientists at NTP had resectioned the pancreas of all test groups in the rat bioassay. The additional sectioning of pancreata resulted in an increased number of tumors in the control animals, thus diminishing the statistical significance of this lesion. Based on this finding, the NTP scientists concluded that the evidence for carcinogenicity in male rats should be downgraded from *clear evidence* to *some evidence*. The CPRC considered the NTP's information and concluded that dichlorvos should remain classified as a Group B2 carcinogen, because: (1) The incidence of mononuclear cell leukemia in dichlorvos 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 dichlorvos treatment; and (3) dichlorvos is a direct acting mutagen. The Committee considered this as an interim classification until the following additional data had been reviewed: (1) the results of a Japanese study in which dichlorvos was administered in drinking water to Fischer 344 rats and B6C3F1 mice; (2) additional data on a chronic rat inhalation study; (3) additional in vivo mutagenicity data, and (4) additional historical control information on pancreatic acinar adenomas.

The CPRC met for a fourth time on July 19, 1989, the conclusions of which serve as the basis for the cancer hazard assessment in this proposed determination (Ref. 7). The purpose of this meeting was to reconsider the NTP rat study in light of the recent NTP Panel of Experts report, evaluate new oncogenicity studies with DDVP administered by inhalation or in drinking water and consider other ancillary information.

As mentioned earlier, the NTP reexamined the pancreata of male and female rats using longitudinal sections which diminished the statistical significance of this lesion. The NTP analysis of the combined data indicated a statistically significant difference between the treated and control groups with a positive dose-related trend using the logistic regression analysis. However, EPA scientists concluded that the increase in pancreatic acinar tumors was neither significant in the Fischer Exact test for pairwise comparison, nor positive in the Cochran-Armitage test for dose-related trend, which are typically used for testing dose groups having no survival disparities. The incidence of animals with multiple pancreatic adenomas was still increased with dichlorvos treatment and outside of the historical control range.

The Committee also reevaluated an inhalation oncogenicity study in which 50 CFE rats/sex/dose were exposed to concentrations of 0.05, 0.5 or 5.0 mg/m³ of technical dichlorvos 23 hours per day for 2 years. This study was reviewed for the dichlorvos Registration Standard and the Agency considered the study inadequate for evaluating the carcinogenicity of the chemical. The study was upgraded after the individual animal data were submitted to the Agency. Agency scientists have concluded that administration of dichlorvos did not alter the tumor incidence in this study.

In addition to the Japanese drinking water study in Fischer 344 rats, Amvac Chemical Corporation submitted a study to the Agency in March 1989, using B6C3F1 mice which was also conducted in Japan. In both studies, dichlorvos was administered in drinking water for 2 years. The CPRC considered both studies to be deficient in conduct and reporting, including incomplete histopathologic evaluation, absence of water consumption data, and failure to include individual animal data in the final report. As a result of these deficiencies, the studies are not amenable to statistical analyses. However, the studies are useful in identifying a qualitative trend in that dichlorvos treatment induced some tumors similar to those induced in the oral gavage studies. In the rat study, there appeared to be an increased incidence of mononuclear cell and lymphocytic leukemia in treated males, as well as mammary gland fibroadenomas in females. In the mouse study, there appeared to be an increased incidence of fibrous histiocytomas and thymomas in males.

The Committee agreed, based upon the available information to reclassify dichlorvos as a Group C carcinogen, in accordance with the Agency's Guidelines for Carcinogenic Risk Assessment. This downgrading from the previous classification as Group B2 was due to: (1) Erosion of the evidence on the pancreatic acinar adenomas in male rats; (2) upgrading and consideration of the negative inhalation study in CFE rats; and (3) questions regarding the biological significance of the primary tumors in the NTP studies, i.e., leukemia in rats (variable tumors in historical controls) and forestomach tumors in mice and its relevance to man.

ii. Weight-of-the-evidence for carcinogenicity. In its most recent evaluation, the fourth cancer peer review, the CPRC considered the weight-of-the-evidence and concluded that dichlorvos should be classified as a Group C (possible human) carcinogen based on inadequate human data and limited data from animal bioassays. The Group C classification is supported by the following points:

(a) In B6C3F1 mice, dichlorvos induced a statistically significant increase in forestomach squamous cell papillomas and combined forestomach squamous cell carcinomas and papillomas in high-dose females. This tumor-type (squamous cell papillomas) was also increased in high-dose males but was significant only for a positive dose-related trend.