(b) In Fischer 344 rats, dichlorvos was associated with a statistically significant increase, with a positive dose-related trend, in leukemia (of all sites and types) in males at both dosage levels. This evidence is supported by the results of the transplantable rat mononuclear cell leukemia model. The treatment was also associated with a numerical (not statistically significant) increase in pancreatic acinar adenomas in males. The incidence of animals with multiple pancreatic acinar adenomas was also increased.

(c) The Group C classification is further supported by studies indicating that dichlorvos is a direct acting gene mutagen in bacteria, fungi and mammalian cells *in vitro*, and suggesting *in vivo* mutagenic activity. (Refs. 8-17). Dichloroacetaldehye, a product of hydrolytic or oxidative cleavage of dichlorvos, has also been reported to be mutagenic in the scientific literature (Ref. 18). Additionally, dichlorvos is structurally similar to known chemical mutagens/ carcinogens (i.e., tetrachlorvinphos and phosphamidon).

iii. Dose-response assessment. The CPRC concluded that a quantitative estimate of the carcinogenic potency should be performed for dichlorvos. Cancer potency (or Q_1^*) is a quantitative estimate of the relationship between exposure to increasing doses of a chemical and the chemical's ability to induce tumors (i.e., increased number of tumors per unit dose). Because most animal studies do not include a sample size large enough to detect carcinogenic responses at low doses comparable to environmental exposures, the Agency normally estimates the cancer potency of a chemical by extrapolating from responses in high-dose animal experiments.

Several mathematical models have been developed to estimate the cancer potency. In the absence of information demonstrating a more appropriate model, the Agency generally uses the linearized multi-stage model to extrapolate from effects seen at highdoses in laboratory studies to predict tumor response at low-doses. This model is based on the biological theory that a single exposure to a carcinogen can initiate an irreversible series of transformations in a single cell that will eventually lead to a tumor. In addition, the linearized multi-stage model assumes that the probability of each transformation is linearly related to the degree of exposure (i.e., a threshold does not exist for carcinogenicity).

Using this model, the Agency estimated the cancer potency (Q_1^*) for dichlorvos based on the tumor

incidence data in female mice and male rats in the NTP studies. The cancer potency in human equivalents is 1.22×10^{-1} (mg/kg/day)⁻¹, which is the geometric mean of the Q_1^* for female mouse forestomach tumors and the Q_1^* for leukemia in male rats (Ref. 19). The Q_1^* represents the 95 percent upper confidence limit of tumor induction likely to occur from a unit-dose.

The CPRC (fourth cancer peer review) also recommended not to quantify the cancer risk by a low-dose extrapolation model for the inhalation route of exposure. The primary basis for this recommendation was the upgrading of a 2-year inhalation study in rats which did not result in an increased tumor incidence. The recommendation was based on the following considerations: The quality of the oral cancer data, the route specificity of the target organs, the reliability and accuracy in estimating the target-dose and the unlikelihood that exposure via the inhalation route would lead to the formation of a reactive metabolite.

In addition, the OPP Reference Dose Committee concluded that extrapolating the results from the oral gavage studies to the dermal route of exposure is not appropriate for dichlorvos (Ref. 20). This decision was based on the following considerations: (1) There was no dose-response relationship in the leukemia observed in male Fisher 344 rats; (2) the tumors observed in female B6C3F1 mice were contact site tumors, the relevance of which to humans is unknown, and the incidence of which, at all dose levels, including the concurrent controls, was outside the National Toxicology Program's control range; (3) the dynamics of absorption, distribution, metabolism and excretion do not favor retention of the chemical in animal tissues and makes it difficult to determine accurately the concentration at the target site; and (4) it is not expected that topically applied doses would reach the target organ(s) in sufficient quantity to produce a carcinogenic response or would be sufficient to alkylate macromolecules in the target tissues to produce contact site tumors. Therefore, extrapolation from oral data to dermal or inhalation routes is not appropriate, for estimation of excess individual cancer risk, for exposure to dichlorvos.

2. Cholinesterase inhibition. Cholinesterase (ChE) refers to a family of enzymes that are essential to the normal functioning of the nervous system. These enzymes are necessary for the transmission of nerve impulses. Inhibition of ChE activity can result in a number of cholinergic signs and symptoms in humans, depending on the rate and magnitude of exposure, including: Headaches, dizziness, nausea, vomiting, diarrhea and increased urination, blurred vision, pinpoint pupils, increased salivation, labored breathing, muscle paralysis, slow heart rate, respiratory depression, convulsions, coma and even death. These enzymes have been identified in nearly every tissue of the body; however, ChE activity is usually measured in blood plasma and red blood cells in humans, while ChE levels in laboratory animals are measured in plasma, red blood cells as well as brain tissue

Organophosphate pesticides, such as dichlorvos, are known to inhibit ChE activity and some cause delayed neurotoxic effects. EPA has evaluated the available information and concluded that dichlorvos is a potent ChE inhibitor. This determination is based on toxicological data using laboratory animals, human poisoning incidents, and limited human toxicity information, which are discussed below.

i. Laboratory data. Acute, subchronic and chronic laboratory studies using experimental animals have shown dichlorvos to be a potent ChE inhibitor, significantly reducing blood plasma, red blood cell and brain ChE. ChE inhibition has been demonstrated in several mammalian species following oral, inhalation, and dermal administration of dichlorvos. Only the primary studies selected for use in assessing risk from short-term, intermediate, and long-term exposures are discussed below.

(a) Acute toxicity data. Acute neurotoxicity data are limited in comparison to available subchronic and chronic data, but are more relevant for assessing risk from single and shortterm repeated exposure scenarios. Acute neurotoxicity studies have been conducted in both hens and rats. An acute neurotoxicity study in rats evaluated the neurobehavioral signs and the neuropathological effects following single exposures, but did not measure ChE inhibition (Ref. 21). Groups of 12 male and female Sprague-Dawley rats were administered single oral doses of 0, 0.5, 35 or 70 mg/kg/day by gavage. At the mid- and high-doses, administration of dichlorvos resulted in a variety of neurological and physiological changes (e.g., alterations in posture, mobility and gait, reduced or absent forelimb/ hindlimb grasp, tremors). Most of these changes were observed about 15 minutes after compound administration, while no toxicity was apparent for the survivors (there were several deaths at the high-dose) 7 days following administration of dichlorvos at all dose