were statistically significant reductions in plasma, RBC and brain ChE activity at 1.25 and 6.25 μ g/L, while at 0.25 μ g/ L ChE activity was depressed less than 15 percent. The NOEL for this study is 0.25 μ g/L based on ChE inhibition in plasma, RBC and brain tissue. The NOEL of 0.25 μ g/L corresponds to approximately 0.14 mg/kg/day. In converting from μ g/L to mg/kg/day, EPA assumed that 100 percent of the dichlorvos vapor is absorbed by inhalation and also that the rabbit breathing rate is constant over time.

Additional information on neuropathological effects can be drawn from a 28-day delayed neurotoxicity study in hens, from which preliminary results were submitted to the Agency (Ref. 28). This study was required based on the results of the acute study in hens discussed above. Groups of 21 hens were administered dichlorvos orally at doses of 0, 0.3, 1.0, or 3.0 mg/kg/day for 28 days. These data suggest that significant axonal degeneration in the spinal cord occurred following oral administration of 1 and 3 mg/kg/day, while at 0.3 mg/kg/day only minor effects were noted. While such findings must be regarded as preliminary, they should be regarded as potentially serious, since such lesions represent an irreversible and relatively serious effect. In addition, this report notes that significant (34 to 63 percent) brain ChE inhibition was seen at 1 and 3 mg/kg/ day. The final report was submitted to the Agency and is currently under review.

(c) Chronic toxicity data. Both oral and inhalation toxicity data demonstrate that long-term exposure to dichlorvos results in plasma, RBC, and brain ChE inhibition. In a chronic rat inhalation study, groups of 50 male and 50 female CFE rats per dose level were exposed to 0, 0.05, 0.48, or 4.7 mg/m3 of dichlorvos for 2 years (Ref. 29). There was a statistically significant decrease in ChE activity in plasma, red blood cells, and brain in the mid- and high-dose groups (76, 72, 90 percent and 83, 68, 90 percent of control activity in mid-dose males and females; and 38, 4, 21 and 22, 5, 16 percent of control activity in highdose males and females, respectively). Red blood cell ChE was reduced to 88 percent of control activity in females dosed at 0.05 mg/m³, but this decrease was not statistically significant. The NOEL was established at 0.05 mg/m³ based on ChE inhibition in plasma, red blood cells and brain tissue. The concentration of 0.05 mg/m³ corresponds to approximately 0.055 mg/ kg/day, assuming a constant breathing rate in rats and 100 percent absorption of dichlorvos vapor.

Groups of 4 male and 4 female dogs were administered dichlorvos by capsule 7 days per week at doses of 0, 0.05 (0.1 for the first 3 weeks of study), 1.0 or 3.0 mg/kg/day for 1 year (Ref. 30). Plasma ChE was inhibited (21.1 to 66.6 percent) in males and females in the 0.1, 1.0, and 3.0 mg/kg/day groups during week 2. The low-dose was consequently reduced to 0.05 mg/kg/day on day 22 due to the plasma ChE inhibition (26 percent in females) noted after 12 days of dichlorvos administration. Red blood cell ChE was only slightly decreased (less than 2 percent) in the 0.1 mg/kg/ day group at week 2, while animals in the 1.0 and 3.0 mg/kg/day groups exhibited RBC ChE inhibition of 33 to 75 percent. Statistical analyses were not conducted prior to week 13. Statistically significant depression in plasma and RBC ChE occurred at week 13 in males and females in the 1.0 and 3.0 mg/kg/ day groups. In addition, brain ChE was significantly reduced in males and females in the high-dose group and in the males of the mid-dose group at termination. Brain ChE activity was inhibited approximately 22 percent in males in the 1.0 mg/kg/day group and 47 percent and 29 percent, respectively, in males and females in the 3.0 mg/kg/ day group compared to controls. Study results correspond to a NOEL of 0.05 mg/kg/day, based on plasma, RBC, and brain ChE inhibition.

A two-generation reproductive study was conducted in which Sprague-Dawley rats were exposed via the drinking water to dichlorvos at concentrations of 0, 5, 20, or 80 ppm (males - 0.5, 1.9 or 7.2 mg/kg/day; females - 0.6, 2.3, or 8.3 mg/kg/day) (Ref. 31). ChE assays (plasma, RBC and brain) were performed on males and females of both the F_0 and F_1 generations at terminal sacrifice. The data indicate that RBC ChE was inhibited in both males and females at all doses and in a dose-related manner. At the low-dose, RBC ChE activity was decreased 7 to 14 percent in males and 17 to 23 percent in females. RBC ChE inhibition was statistically significant for both males and females at all dose levels, except for the F₀ males at 0.5 mg/ kg/day (7 percent inhibition). Plasma ChE inhibition was statistically significant for both males and females at the mid- and high-dose levels. The plasma ChE inhibition for F1 males at the low-dose (0.5 mg/kg/day) was also statistically significant (15 percent). In addition, brain ChE activity was inhibited in males and females of both generations at all dose levels. Statistically significant reductions occurred only at the mid- and highdoses. The study results establish a NOEL of less than 5 ppm for RBC and plasma ChE inhibition (males - 0.5 mg/ kg/day; females - 0.6 mg/kg/day).

ii. Human data—(a) Toxicity data. EPA reviewed several studies in the scientific literature that measured ChE inhibition in humans following exposure to dichlorvos (Ref. 32). The studies only covered a few exposure scenarios, including occupant exposure to resin pest strips and workers reentering treated warehouses. There were few, if any, adverse effects following most resin pest strip exposures. Only one headache was reported which may have been associated with dichlorvos exposure. Usually only plasma ChE inhibition was statistically significant with statistically significant RBC ChE inhibition occurring only rarely. However, interpretation of the study results is difficult because of methodological problems and utilization of outdated methods for measuring ChE activity. In addition, the studies only examined small numbers (less than 20) in any one test group.

(b) Poisoning incidents. Exposure to dichlorvos has resulted in poisoning incidents. Although the number of incidents is not large, it is sufficient to be of concern and can be viewed as confirmatory of the inadequate MOEs. Several sources are available indicating that exposure to dichlorvos has resulted in poisoning incidents. As part of the assessment for the dichlorvos Registration Standard, the Agency reviewed the Pesticide Incident Monitoring System (PIMS) data base covering a period from 1964 to 1980 (Ref. 33). Only 182 of the 598 dichlorvos incidents could be identified as involving products that contained dichlorvos as the sole active ingredient. A majority (147) of these 182 reports involve humans and domestic animals in the home environment, with 114 incidents resulting from ingestion and application of dichlorvos. One death was reported. Ingestion incidents usually involved children chewing flea collars and resin pest strips. Most of the application incidents involved situations where the existing label precautions were not followed. Of the remaining 416 incidents in which dichlorvos was cited in combination with other chemicals, there were 9 human fatalities reported. EPA's Incident Data System, in operation since June 1992, does not contain any human poisoning incidents attributed to dichlorvos exposure.

Case reports from the California Pesticide Illness Surveillance Program are available for dichlorvos from 1982 to