levels. Based on the study results, the NOEL for signs associated with ChE inhibition was established at 0.5 mg/kg/day.

An acute delayed neurotoxicity study in hens resulted in cholinergic signs of ChE inhibition and neuropathic effects (Ref. 22). Ten birds were administered a single dose of 16.5 mg/kg/day by oral intubation. The test birds were given another oral dose at 21 days and observed for an additional 21 days. Dichlorvos-treated birds demonstrated signs of ChE inhibition shortly after dosing, including: lethargy and depression, incoordination, limb weakness, wing drop, and reduced reaction to external stimulation. The birds were asymptomatic by day 3 after dosing. Administration of dichlorvos did not produce overt signs of acute delayed neurotoxicity, but neuropathic effects (peripheral nerve lesions which are associated with paralysis) did occur in one hen. A NOEL was not shown for this effect in this one dose study.

Additional information about shortterm exposure is provided by a rangefinding study in which dogs (one male and one female for each dose) were administered dichlorvos by capsule for 2 weeks at the following doses: 0, 0.1, 1.0, 5.0, 10, 15, 30, or 60 mg/kg/day (Ref. 23). Plasma and red blood cell ChE levels were decreased in the 1.0 mg/kg/ day group and above as early as 6 days after dosing. The degree of ChE inhibition increased with dose. During the first week following dosing, severe cholinergic signs were observed in animals at 30 and 60 mg/kg/day and death occurred at these doses during the second week of dosing. However, this study is not appropriate for short-term risk assessment because only a limited number of animals were treated at each dose and dichlorvos was administered repeatedly. This study indicates that short-term exposure to dichlorvos at low levels produces ChE inhibition in plasma, red blood cells and brain tissue, and contributes to the overall weight-ofthe-evidence.

(b) Subchronic toxicity data. A study was performed in rats providing ChE inhibition data following subchronic exposure to dichlorvos (Ref. 24). Groups of 10 male and 10 female rats were administered doses of 0, 0.1, 1.5 or 15 mg/kg/day by oral gavage for 13 weeks (5 days/week). Observations recorded approximately 30 to 60 minutes postdose included salivation in 7 males and 4 females treated with 15 mg/kg/day. Urine stains were also seen in 7 males and 5 females at this dose. These observations were seen on certain days during weeks 6 through 12 for males and 8 through 12 for females. At week

7, plasma ChE activity was significantly reduced in mid- and high-dose male and high-dose female rats when compared to the controls. Mid- and high-dose male and female rats also demonstrated significantly reduced red blood cell (RBC) ChE activity when compared to the controls at 7 weeks. At the 14-week interval, plasma ChE activity was significantly reduced in high-dose males and females, while RBC activity was significantly lower than controls in midand high-dose animals. Red blood cell ChE activity was also reduced in lowdose (0.1 mg/kg/day) females at 14 weeks; however, the RBC ChE inhibition was not considered biologically significant since it was less than 10 percent below ChE activity in control animals. Brain ChE activity in high-dose female rats was 49 percent lower than in control females and was statistically significant, while brain ChE activity in high-dose males was reduced 28 percent below control males but inhibition was not statistically significant. The data presented support a NOEL of 0.1 mg/kg/ day based on plasma and red blood cell ChE inhibition at doses of 1.5 mg/kg/ day and above.

An additional subchronic study in rats evaluated neurobehavioral signs, neuropathological effects, and also measured ChE activity (Ref. 25). Dichlorvos was administered by oral gavage to male and female rats at doses of 0, 0.1, 7.5, or 15 mg/kg/day (15 animals/sex/dose) for 90 days. There were no significant differences between the control and treated animals with respect to the functional observational battery or locomotor activity evaluations, nor were any neuropathological lesions attributable to dichlorvos. However, administration of dichlorvos was accompanied by cholinergic signs (tremors, salivation, exophthalmos, lacrimation) approximately 15 minutes after dosing in the high-dose animals and, to a lesser extent, in the mid-dose animals. In general, cholinergic signs occurred during the first dosing week in highdose animals and during the third dosing week in mid-dose animals and persisted to study termination in both groups. Plasma ChE inhibition was statistically significant at all time periods measured; however, RBC ChE inhibition was only statistically significant for high-dose males at week 3. ChE levels in RBC were reduced 23, 12, and 18 percent in the mid-dose males and 35, 8, and 11 percent in the high-dose males compared to controls during weeks 3, 7, and 13, respectively. In females, RBC ChE inhibition of 13, 38, and 33 percent at the mid-dose, and

of 4, 42, and 35 percent at the high-dose were noted during weeks 3, 7, and 13, respectively. Brain stem and brain cortex ChE activity were also reduced from 11 to 12 percent in low-dose animals and from 10 to 16 percent in high-dose rats as compared to controls. Inhibition of brain stem ChE activity was statistically significant in high-dose males only, while in the cerebral cortex ChE was significantly reduced for animals in the mid- and high-dose groups. The NOEL from this study was 0.1 mg/kg/day based on ChE inhibition (plasma, RBC, brain) and cholinergic signs occurring at 7.5 mg/kg/day.

A developmental toxicity study in New Zealand white rabbits produced signs of ChE inhibition at similar dose levels as the subchronic rat studies (Ref. 26). Groups of 16 pregnant females were administered doses of 0, 0.1, 2.5, or 7.0 mg/kg/day by oral gavage on gestation days 7 through 19, inclusive. The doses were selected based on the results of a range-finding study conducted in the same strain of pregnant rabbits at dose levels of 0, 0.1, 1.0, 2.5, 5.0 or 10 mg/ kg/day (8 per group, except for 7 in the 2.5 mg/kg/day group) in which there were statistically significant reductions in maternal plasma and RBC ChE activity in a dose-related manner at all doses except 0.1 mg/kg/day. Profound treatment-related maternal mortality (5/ 8 died) and cholinergic signs occurred at 10 mg/kg/day. In the definitive developmental toxicity study, mortality was observed at 2.5 mg/kg/day (13 percent) and 7.0 mg/kg/day (25 percent). ChE inhibition was not measured; however, apparent anticholinesteraserelated signs and symptoms were observed at the high-dose, including ataxia, prone positioning, tremors, excitation, salivation, diarrhea and difficulty in breathing. Based on the range-finding and definitive study results, the maternal toxicity NOEL and Lowest Effect Level (LEL) were demonstrated at 0.1 and 2.5 mg/kg/day, respectively.

An inhalation developmental toxicity study in rabbits produced findings similar to those of the oral developmental toxicity study (Ref. 27). Groups of 20 female Dutch rabbits were exposed to 0, 0.25, 1.25, or 6.25 µg/L of dichlorvos for 23 hours per day, from day 1 of mating to gestation day 28. No cholinergic signs were noted at 0, 0.25, or 1.25  $\mu$ g/L, but severe toxicity and mortality occurred after the 6th day of exposure to 6.25 µg/L. Cholinergic signs observed included anorexia, lethargy, muscular tremors, mucous nasal discharge and diarrhea. Sixteen of the 20 does at the high-dose died or were killed because of intoxication. There