1990 (Ref. 34). A total of 78 poisoning incidents were attributed to dichlorvos exposure. Sixty were classified as systemic poisonings, 12 caused eye problems and the remaining 6 resulted in skin irritation. The majority of these incidents involved active ingredients in addition to dichlorvos. In addition, poisonings were attributed to both occupational and residential exposures.

Finally, the American Association of Poison Čontrol Centers (AAPCC) reported that for the years 1985 - 1992 there were 21,006 exposures of all kinds for dichlorvos alone and 21,844 exposures for dichlorvos alone and in combination with other active ingredients (Refs. 35 and 36). Of the 21,006 exposures, 2,671 individuals were treated and released and 350 were hospitalized. There were 259 occupational cases involving dichlorvos alone and an additional 57 occupational cases involving dichlorvos in a mixture with another pesticide. Of the 259 cases, 99 workers were treated and released and 13 were hospitalized. Only one of the occupational cases was considered life-threatening, while 10 of the nonoccupational cases were so categorized.

iii. Animal health and safety data. EPA reviewed 3 animal heath and safety data studies which examined the effect on dogs and cats of wearing registered cat and dog flea collar products. These studies provide strong evidence that dichlorvos, used in combination with other active ingredients, has a significant effect on reducing ChE activity in dogs. Although the ChE inhibition could result in part from another pesticide active ingredient, the Agency has no data to disprove that ChE depression is a result of dichlorvos exposure (Refs. 37-39).

In the first study, groups of 3 male and 3 female dogs per group served either as controls, or wore 1, 3, or 5 collars containing 9.3 percent dichlorvos and 4.2 percent chlorpyrifos. In the 1-collar group, 5 out of 6 dogs averaged RBC ChE inhibition (statistically significant) of 20 to 30 percent during the period day 3 through week 2. Plasma ChE inhibition was even greater, averaging 65.6 percent as compared to pre-test values during the perod day 3 through week 4 in 5 animals.

Another study was conducted in which 3 male and 3 female dogs were each assigned to a control group, a group wearing a collar containing 7.8 percent dichlorvos and 4.34 percent chlorpyrifos, a group wearing a collar containing 8.87 percent dichlorvos and 4.44 percent chlorpyrifos, and a group wearing an 8 percent chlorpyrifos collar. The mean percentage plasma ChE activity was significantly different from that of the control group among dogs wearing collars containing dichlorvos from day 7 through week 6. Differences in RBC ChE activity were not statistically significant. More specifically, in animals wearing the product containing 7.8 percent dichlorvos, plasma and RBC ChE activity were inhibited 49 percent and 19 percent as compared to pre-test values. This study demonstrates that plasma and RBC ChE inhibition also can occur from use of these products.

In the last study, ChE activity was measured in dogs over a 98-day period, during which time the dogs wore a placebo collar or 1, 3, or 5 collars containing a mixture of 7 percent dichlorvos and 9 percent propoxur. There was a considerable drop in plasma ChE activity in the first 7 days of exposure (in 1-collar dogs by 30 percent, in 3-collar dogs by 57 percent, and in 5-collar dogs by about 63 percent). In the 1-collar exposure group there was essentially complete plasma ChE recovery by day 56; however, in the 3 and 5-collar females there was still significant plasma ChE inhibition (35 and 43 percent, respectively) on day 98. There was no evidence of any RBC ChE inhibition in any group at any time during this study.

iv. Dose-response assessment. Results from acute, subchronic, and chronic toxicity studies have shown dichlorvos to be a potent inhibitor of plasma, RBC, and brain ChE. In most instances, inhibition of brain ChE occurred at similar doses as plasma and RBC ChE inhibition. Moreover, cholinergic signs were usually associated with actual measurements of ChE inhibition. Neurotoxicity data indicate a correlation between ChE inhibition and neuropathological effects. Overall, the various indicators of ChE inhibition (i.e., altered ChE activity in plasma, RBC, brain, neuropathological effects or cholinergic signs) are observed within a relatively narrow dose range. In addition, the effects indicative of ChE inhibition observed in laboratory studies are further validated by actual human poisonings accompanied by cholinergic signs.

Dose-response data for ChE inhibition and/or cholinergic signs are available for acute, subchronic, and chronic toxicity studies using rats, rabbits, dogs and hens as the test species. EPA selected the lowest NOELs from acute, subchronic, and chronic toxicity studies to calculate MOEs of exposure for individuals exposed to dichlorvos for varying durations of time. The NOELs are based on either brain ChE inhibition and/or cholinergic signs following administration of dichlorvos by the oral and inhalation routes of exposure. Neurotoxicity data following dermal administration of dichlorvos are not available.

(a) Acute/short-term exposure. EPA scientists believe that a NOEL of 0.5 mg/ kg/day is most suitable for calculating MOEs of exposure for acute dietary and short-term occupational or residential (1 to 7 days) exposure scenarios. This NOEL is based on the acute neurotoxicity study in rats resulting in neurological and physiological changes observed shortly after dosing, including alterations in posture, mobility, and gait, reduced or absent forelimb/ hindlimb grasp, increased time to first step, pupillary constriction, tremors, clonic convulsions, increased response time, catalepsy, and reduction in body temperature at 35 mg/kg/day. ChE activity was not measured in this study. There is some uncertainty with this acute NOEL because of the wide gap between dose levels (0, 0.5, 35, or 70 mg/kg/day). Since there are no intermediate doses between the no effect level of 0.5 mg/kg/day and the next level, 35 mg/kg/day, at which a variety of behavior changes were seen, it is possible that additional data might result in a slightly higher NOEL. However, Agency scientists do not believe that such a new acute NOEL would differ greatly from 0.5 mg/kg/day because short-term exposure data from other studies yielded similar results.

(b) Intermediate exposure. EPA selected a NOEL of 0.1 mg/kg/day for assessing intermediate occupational and residential exposure (1 week to several months) to dichlorvos. This NOEL was derived from examining several oral and inhalation toxicity studies. In the subchronic rat neurotoxicity study, administration of dichlorvos at 7.5 mg/ kg/day inhibited plasma, RBC, and brain ChE activity, as well as producing cholinergic signs during the third week of dosing. Based on these findings, a NOEL was established at 0.1 mg/kg/day. The inhalation developmental toxicity study in rabbits demonstrated a NOEL of 0.14 mg/kg/day (converted from 0.25µg/L) based on statistically significant plasma, RBC and brain ChE inhibition occurring at 0.71 mg/kg/day. A maternal toxicity NOEL of 0.1 mg/kg/day was demonstrated in the oral developmental toxicity study in rabbits, based on the results of the range-finding and definitive studies. In the range-finding study, statistically significant plasma and RBC ChE inhibition occurred at all doses except 0.1 mg/kg/day, while cholinergic signs occurred at 2.5 mg/kg/ day and above. ChE inhibition was not measured in the definitive study, but 2