2. A voluntary human study with chronic ChE NOEL of 0.03 mg/kg/day (based on 20 days of exposure at this level).

3. A 2-year mouse chronic toxicity/ carcinogenicity study with a NOEL of 15 ppm for systemic effects (equivalent to 2.25 mg/kg/day) and no carcinogenic effects observed under the conditions of the study at all levels tested (0, 0.5, 5, and 15 ppm, equivalent to 0.075, 0.75, and 2.25 mg/kg/day).

4. A voluntary human study with acute ChE NOEL of 0.10 mg/kg/day (based on daily single-dose exposures of 0, 0.014, 0.03, or 0.10 mg/kg/day) determined at 1, 3, 6, and 9 days of treatment.

5. A 2-year rat feeding/carcinogenicity study with ChE NOEL of 0.1 and LEL of 1.0 mg/kg/day (based on decreased plasma and brain ChE activity), and a systemic NOEL of 1.0 mg/kg/day and LEL of 10 mg/kg/day (based on decreased erythrocyte and hemoglobin values and increased platelet count during the first year). There were no observed carcinogenic effects at the levels tested (0.05, 0.1, 1.0, and 10 mg/ kg/day) under the conditions of the study. Chlorpyrifos is classified as a Group E chemical (no evidence of carcinogenicity).

6. A three-generation reproduction study in rats with no reproductive effects observed at the dietary levels tested (0, 0.1, 0.3, and 1.0 mg/kg/day).

7. Two rat developmental toxicity studies: one negative for developmental toxicity at all dose levels (levels tested were 0.1, 3.0, and 15.0 mg/kg/day); and one with maternal NOEL of 15 mg/kg/ day and developmental NOEL of 2.5 mg/kg/day (levels tested, by gavage, were 0, 0.5, 2.5, and 15 mg/kg/day).

8. A mouse developmental toxicity study with a teratogenic NOEL greater than 25 mg/kg/day (highest dose tested) and a developmental fetotoxic NOEL of 10 mg/kg/day and LEL of 25 mg/kg/day (decreased fetal length and increased skeletal variants).

9. A developmental toxicity study in rabbits with maternal and developmental NOELs of 81 mg/kg/day, and maternal and developmental LELs of 140 mg/kg/day (based on maternal decreased food consumption on gestation day 15 to 19, and body weight loss during the dosing period followed by a compensatory weight gain; and based on a slight reduction in fetal weights and crown-rump lengths, and fetal increased incidence of unossified fifth sternebrae and/or xiphisternum). Levels tested were 0, 1, 9, 81, and 140 mg/kg/day. 10. An acute delayed neurotoxicity study in the hen that was negative at 50 and 100 mg/kg/day.

11. Several mutagenicity studies which were all negative. These include an Ames assay, two Chinese hamster ovary cell mutation assays, a micronucleus assay for chromosomal aberration, an in vitro chromosomal aberration assay with and without enzymatic activation, and an unscheduled DNA synthesis assay.

12. A general metabolism study in rats shows that the major metabolite of chlorpyrifos is 3,5,6-trichloro-2pyridinol (TCP). The studies listed below were conducted to demonstrate that TCP is less toxic than chlorpyrifos and is not a ChE inhibitor.

a. A 90-day rat feeding study with a systemic NOEL of 30 mg/kg/day. Levels tested were 0, 10, 30, and 100 mg/kg/day.

b. A rat developmental toxicity study with no developmental toxicity observed at the dosages tested (0, 50, 100, and 150 mg/kg/day).

c. Mutagenicity studies (including an Ames assay and an unscheduled DNA synthesis assay) were negative for mutagenic effects.

Based on the above studies, the Agency has concluded that the TCP metabolite is not of toxicological concern.

For the assessment of chronic dietary risk, the reference dose (RfD) based on the human voluntary ChE study (ChE NOEL of 0.03 mg/kg/day) and using a 10-fold uncertainty factor is calculated to be 0.003 mg/kg of body weight/day. Tolerances for food uses appear in 40 CFR 180.342 and 40 CFR 185.1000. The Dietary Risk Exposure Section (DRES) used, when justified and appropriate, anticipated residues rather than published tolerance values, and data regarding percent crop treated (when less than 100%). The anticipated residue contribution (ARC) from published uses of chlorpyrifos is 0.000860 mg/kg of body weight/day for the overall U.S. population. This represents 28.7% of the RfD. None of the DRES subgroups has an exposure that exceeds the RfD. The population subgroup most highly exposed is nonnursing infants, less than 1 year old, with an ARC from published uses of 0.002147 mg/kg of body weight/day, 71.6% of the RfD. The next most highly exposed population subgroup is children, 1 to 6 years old, with an ARC from published uses of 0.001914 mg/kg of body weight/day, 63.8% of the RfD. The proposed tolerance on oats does not raise the ARC as a percentage of the RfD because the oats are not to be used for human food and any secondary residues

occurring in milk, eggs, or meat of livestock and poultry will fall within existing tolerances for these commodities. The ARC was calculated assuming tolerance level residues of chlorpyrifos on these commodities.

The DRES detailed acute analysis estimates the distribution of single-day exposures for the overall U.S. population and certain subgroups. The analysis evaluates individual food consumption as reported by respondents in the USDA 1977-1978 Nationwide Food Consumption Survey (NFCS) and accumulates exposure to the chemical for each commodity. Each analysis assumes uniform distribution of chlorpyrifos in the commodity (oats). Since the toxicological endpoint to which exposure is being compared in this analysis is neurotoxicity, four human population subgroups (infants, less than 1 year old; children, 1 to 12 years old; females, 13 years old and older; males, 13 years old and older), as well as the overall population, are of interest

The Margin of Exposure (MOE) is a measure of how close the high-end exposure comes to the NOEL and is calculated as the ratio of the NOEL to the exposure. (NOEL/exposure = MOE.) For neurotoxicity, the Agency is generally not concerned unless the MOE is below 10 when the NOEL is based on human data. For the overall population the calculated MOE at high end (topmost eaters-defined as the top 0.5% of the population in terms of consumption) as a result of all commodities, other than oats, treated with chlorpyrifos is less than 10. In the overall population 6% of consumers have an MOE less than 10.

The DRES analysis to estimate the potential increased risk of neurotoxicity resulting from residues of chlorpyrifos in meat, poultry, eggs, and milk obtained from animals fed treated oats indicates that the MOE is greater than 10 for the overall U.S. population and for each of the 4 population subgroups. The calculated MOE at high end (topmost eaters—in this case defined as the top 0.5% of the population/ subpopulation in terms of consumption) for the overall population is 33; for infants, less than 1 year old it is 20; for children, 1 to 12 years old it is 25; for females, 13 years old and older it is 83; and for males, 13 years old and older it is 71.

The Margin of Exposure estimates are considered conservative because a major assumption is that the high-end eater consumed only meat, poultry, eggs, and/ or milk from animals fed only oats containing chlorpyrifos residues. The increase in calculated estimates of acute