

classification of pyridalyl will be "E" (no evidence of carcinogenicity for humans).

6. *Animal metabolism.* Rats metabolize and rapidly eliminate ^{14}C S-1812. Most of the administered dose was eliminated within 48 hours mainly in the feces. There were no apparent sex-related differences in either the rate of elimination of ^{14}C S-1812 or in the metabolite distribution. There was no apparent enzymatic induction as the metabolic pattern was unchanged by multiple (14-day) administrations of ^{14}C S-1812 at 5 mg/kg/day.

7. *Metabolite toxicology.* Two metabolites of pyridalyl, 2-hydroxy-5-trifluoromethylpyridine (HTFP) and HPDO that occur in extremely low levels in plants and animals, were also tested for genetic toxicity. Each metabolite was tested in an *in vitro* bacterial (Ames test) and mammalian HGPRT assay mutagenesis assay as well as in an *in vitro* chromosome aberration test. Both metabolites were positive in the bacterial assay, but were negative in the mammalian mutagenesis assay. One metabolite, HPDO, was positive in the chromosome aberration test. The biological significance of this finding is uncertain given that only low levels of these compounds are detectable in plants or animals and that pyridalyl does not appear to be carcinogenic at high and chronic doses.

8. *Endocrine disruption.* Data from the rat reproduction and subchronic studies indicated that pyridalyl may effect lipid metabolism and, consequently, hormone levels. These *in vivo* results suggested that S-1812 may have a modulating activity on steroid biosynthesis at doses generally exceeding MTD.

To further understand these findings, two additional, non-guideline, mechanistic studies were conducted. A detailed analysis of the effect of S-1812 on serum steroid hormone levels was performed in rats exposed for 4 weeks to dose levels equivalent to those used in the rat reproduction study. And an *in vitro* study was conducted in rat primary Leydig cell and ovary cell cultures to investigate the effects of S-1812 on the production of hormones and on the activity of enzymes that catalyze sex steroid hormone biosynthesis. These studies support the conclusion that S-1812 is not an endocrine disruptor in *in vivo* mammalian systems. Although, very weak inhibition of a single steroid biosynthesis pathway was observed in the *in vitro* study, effects possibly related to this conversion in mammalian systems were observed only at dose levels that greatly exceeded the maximum tolerated dose.

C. Aggregate Exposure

1. *Dietary exposure.* Acute and chronic dietary analyses were conducted to estimate exposure to potential pyridalyl residues in or on the following crops and crop groups: Cottonseed, turnip greens, vegetables, leafy, except Brassica, group 4, Brassica, group 5 and vegetables, fruiting, group 8, using the Cumulative and Aggregate Risk Evaluation System (CARES) Version 1.3. Exposure estimates to water were made based upon modeling First Index Screening Tool Reservoir (FIRST model).

i. *Food—acute.* The acute dietary exposure estimate of pyridalyl residues in food at the 99.9th percentile was calculated to be 43% of the acute Reference Dose (aRfD) with a margin of exposure of 235. The population subgroup with the highest exposure was non-nursing infants. The aRfD was defined as the NOAEL from a developmental toxicity study in rabbits and includes an uncertainty factor of 100 (NOAEL = 50 mg/kg body weight (bwt)/day, aRfD = 0.5 mg/kg/day).

b. *Chronic.* The chronic dietary exposure estimate of pyridalyl residues in food at the 100th percentile was calculated to be 1.4% of the chronic Reference Dose (cRfD) with a margin of exposure of 732. The population subgroup with the highest exposure was children 1–2 years old. The cRfD was defined as the NOAEL from the 2-generation reproduction study in rats including an uncertainty factor of 100 (NOAEL = 2.8 mg/kg bwt/day, cRfD = 0.028 mg/kg/day).

These values are based on proposed tolerance level residues adjusted for percentages of the crop treated. No adjustments were made for common washing, cooking or preparation practices and as such are very conservative values.

ii. *Drinking water.* Since pyridalyl is applied outdoors to growing agricultural crops, the potential exists for the parent or its metabolites to reach groundwater or surface water that may be used for drinking water. Screening Concentration in Groundwater (SCIGROW) simulation predicted zero S-1812 concentration in ground water indicating that S-1812 will not leach. This result is expected due to the very high Koc value of pyridalyl. For the surface water FIRST (version 1.0) simulation produced peak day concentration (acute) of 0.15 parts per billion (ppb). The peak FIRST concentration was used for both the acute and chronic exposure assessment. Based on these modeled drinking water concentrations, the worst-case acute/chronic dietary exposure from drinking

water is estimated to be negligible (0.02% of the aRfD, and 0.003% of the cRfD for children).

2. *Non-dietary exposure.* Pyridalyl is proposed only for agricultural uses and no homeowner or turf uses. Thus, no non-dietary risk assessment is necessary.

D. Cumulative Effects

Section 408(b)(2)(D)(v) requires that the Agency must consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity." Available information in this context include not only toxicity, chemistry, and exposure data, but also scientific policies and methodologies for understanding common mechanism of toxicity and conducting cumulative risk assessments. For most pesticides, although, the Agency has some information in its files that may turn out to be helpful in eventually determining whether a pesticide shares a common mechanism of toxicity with any other substances, EPA does not at this time have methodologies to resolve the complex scientific issues concerning common mechanism of toxicity in a meaningful way for most registered pesticides.

E. Safety Determination

1. *U.S. population.* Using the conservative assumption described above, based on the completeness and reliability of the toxicity data, it is concluded that aggregate exposure to the proposed uses of pyridalyl will utilize at most 43% of the acute RfD and 2% of the chronic RfD for the U.S. population and is likely to be much less, as more realistic data and models are developed. The Agency has no cause for concern if total acute residue contribution is less than 100% of the aRfD, because the RfD represents the level at or below which daily aggregate exposure over a lifetime will not pose appreciable risk to human health. Therefore, there is a reasonable certainty that no harm will occur to the U.S. population from aggregate exposure to residues of pyridalyl under the proposed use patterns.

2. *Infants and children.* The toxicological data base for evaluating prenatal and postnatal toxicity for pyridalyl is complete with respect to current data requirements. There are no special prenatal and postnatal toxicity concerns for infants and children, based on the results of the rat and rabbit developmental toxicity studies or the 2-generation reproductive toxicity study in rats. Using the conservative