

results of these studies see the **Federal Register** of July 18, 2000 (65 FR 44453)).

4. *Chronic toxicity*—i. A 1-year chronic feeding study in dogs fed dosages of 0, 1.1, 2.4, 4.9, and 48.7 mg/kg/day with a NOAEL of 2.4 mg/kg/day.

ii. A combination of 2 chronic feeding studies and 1 carcinogenicity study resulted in rats being fed combined dosages of 0, 1.2, 2.4, 7.0, 23, 71, 143, and 221 mg/kg/day (males) and 0, 1.6, 3.1, 7.0, 23, 71, 180, and 221 mg/kg/day (females) with a NOAEL of 1.2 mg/kg/day (males) and 1.6 mg/kg/day (females). An increased incidence of neoplasms occurred at dose levels greater than the maximum tolerated dose (MTD) of greater than or equal to 23 mg/kg/day in the liver, adrenal, pituitary, prostate (males), uterus (females), and ovaries (females) at dose levels greater than or equal to 143 mg/kg/day. In the testes (males), Leydig cell adenomas were seen at the MTD for dose levels greater than or equal to 23.0 mg/kg/day due to the anti-androgenic nature of vinclozolin.

5. *Carcinogenicity*. A carcinogenicity study in mice fed dosages of 0, 2.1, 20.6, 432, and 1,225 HDT mg/kg/day (males) and 0, 2.8, 28.5, 557, and 1,411 (HDT) mg/kg/day (females) with a NOAEL of 20.6 mg/kg/day (males) and 28.5 mg/kg/day.

An increased incidence of neoplasms occurred at dose levels greater than the maximum tolerated dose (> 28.5 mg/kg/day) in the liver of female mice. (For a detailed discussion of the results of these studies see the **Federal Register** of July 18, 2000 (65 FR 44453)).

C. Toxicological Endpoints

EPA determined the following toxicological endpoints as reported in the **Federal Register** Notice of July 18, 2000. That reference provides a complete description of the Agency's rationale for the values assigned.

1. *Acute toxicity*. EPA selected the NOAEL of 6 mg/kg/day. The population subgroup of concern is females (13+) because the endpoint is an *in utero* effect applicable only to females of childbearing age. An uncertainty factor (UF) of 100 was used to account for interspecies extrapolation and intraspecies variation. On this basis, the acute reference dose (arfd) is 0.06 mg/kg/day. EPA determined that a 10X FQPA safety factor is applicable. The acute population adjusted dose (aPAD) is 0.006 mg/kg/day. An acute dose and endpoint were not identified for other population subgroups.

2. *Chronic toxicity*. EPA has established the Reference Dose (RfD) for vinclozolin at 0.012 mg/kg/day. This RfD is based on a NOAEL of 1.2 mg/kg/

day from the combined chronic toxicity/carcinogenicity study in rats. An UF of 100 was used to account for interspecies extrapolation and intraspecies variation. A 10X FQPA safety factor was added resulting in a chronic population adjusted dose (cPAD) of 0.0012 mg/kg/day.

3. *Short- and intermediate-term toxicity*. For short- and intermediate-term dermal and inhalation toxicity, the NOAEL of 3 mg/kg/day from a rat developmental toxicity study was selected for the population subgroup of concern, females (13+). A dermal absorption factor of 25% was used to correct for route-to-route extrapolation (oral to dermal exposure) and a default inhalation absorption factor of 100% was assumed for oral to inhalation exposure. The margin of exposure (MOE) for females (13+), infants and children is 1,000X.

4. *Long-term dermal and inhalation toxicity (cancer and non-cancer)*. For chronic non-cancer and cancer dermal and inhalation toxicity, EPA selected the chronic NOAEL of 1.2 mg/kg/day from the combined rat chronic toxicity/carcinogenicity study. The Q^{1*} calculated in a low-dose linear extrapolation is 2.9×10^{-1} (mg/kg/day). A dermal absorption factor of 25% was used to correct for route-to-route extrapolation (oral to dermal exposure) and a default inhalation absorption factor of 100% was assumed for oral to inhalation exposure. The cancer assessment includes not only the adult U.S. population but also infants and children as well.

5. *Carcinogenicity*. Vinclozolin is classified as a Group C carcinogen based on Leydig (interstitial testicular) cell tumors in a perinatal rat developmental toxicity study. A non-linear (MOE) approach was determined to be appropriate based on a weight-of-the-evidence conclusion that tumor induction is via an anti-androgenic mechanism. Use of the PAD for overall anti-androgenic effects (0.0012 mg/kg/day) is also protective of cancer effects because it is protective of the anti-androgenic effects that are, in effect, precursors to tumor formation.

6. *Overall anti-androgenic effects*. The Agency has determined that use of the most sensitive regulatory toxicity endpoint and the highest UF would be protective of the anti-androgenic effects on all population subgroups caused by vinclozolin including developmental/reproductive effects as well as carcinogenic effects. In the case of vinclozolin, the most sensitive toxicity endpoint/dose and UF are derived from the rat oral chronic/carcinogenicity study, i.e., the NOAEL of 1.2 mg/kg/day

and an UF of 1,000. The PAD of 0.0012 mg/kg/day was used in assessment of risks resulting from the anti-androgenic activity of vinclozolin.

7. *Endocrine disruption*. A series of mechanistic studies (*in vivo* and *in vitro*) were conducted to define the anti-androgenic properties of vinclozolin. The results of these studies showed that vinclozolin elicits the anti-androgenic effects by binding to androgen sensitive organs.

D. Aggregate Exposure

For a detailed discussion of the results of these exposure calculations see the **Federal Register** of July 18, 2000 (65 FR 44453).

1. *Dietary exposure*. The Agency has previously calculated exposures and risks for the canola green beans, meat, milk, poultry and eggs. The same calculations should be applied to re-establishing these tolerances.

i. *Food—a. acute exposure and risk*. Acute dietary risk assessments are performed for a food-use pesticide if a toxicological study has indicated the possibility of an effect of concern occurring as a result of a 1-day or single exposure. The Agency concluded that acute dietary exposure estimates for the only population subgroup of concern, females (13+), that “The very conservatively estimated acute dietary risk (food only) does not exceed the Agency's level of concern (LOC).”

b. *Chronic exposure and risk*. The chronic dietary exposure estimates expressed as a percentage of the cPAD (0.0012 mg/kg/day) were 4% for the U.S. population and 7% for the most highly exposed population subgroup, children (1–6 years old). EPA generally has no concern for exposures below 100% of the cPAD because the cPAD represents the level at or below which daily aggregate dietary exposure over a lifetime will not pose appreciable risk to human health. Therefore, the chronic dietary risk (food only) does not exceed the Agency's LOC.

ii. *For cancer and anti-androgenic risk assessment*. EPA believes that vinclozolin should be classified as a Group C carcinogen. However, due to the relationship between vinclozolin's anti-androgenic properties and its carcinogenic effects, the Agency believes protecting against the anti-androgenic effects would also be protective against potential carcinogenic effects to all population subgroups (including infants and children).

Accordingly, the cPAD will be protective against potential carcinogenic effects as well as the developmental/reproductive effects. The cPAD already incorporates the full, additional 10x