

hyperplastic nodules) at the highest dose tested (17.5 mg/kg bwt/day), when data for male and female rats were combined.

Since that time, the compound has been reevaluated. The Agency now considers it more appropriate to separate data for males and females and also to separate hyperplastic nodules from tumors (adenomas and carcinomas). When a reevaluation of the hepatic lesions for males and females was performed separately with the elimination of hyperplastic nodules, the data did not demonstrate a statistically significant increased incidence in adenomas and/or carcinomas in either sex. Moreover, the mouse oncogenicity study did not demonstrate oncogenic potential at dose levels up to and including a dose level of 85.7 mg/kg bwt/day (the highest dose level tested).

Because of the appearance of a low incidence of fatty change of the liver (nonneoplastic pathological lesions) in the low-dose groups in this study, it was unclear if a NOEL for fatty change of the liver was established in this study.

3. Additional 2-year chronic feeding/ oncogenicity studies in rats using dietary concentrations of 0, 12.5, 25, and 50 ppm (equivalent to doses of 0, 0.63, 1.25, and 2.5 mg/kg bwt/day). The purpose of these additional studies was to assist in determining a NOEL for fatty liver changes. The first of these two studies was compromised, however, by an outbreak of chronic respiratory disease which reduced survival in all experimental groups, including controls. The study was then repeated with the same dose levels. In the second study, no fatty liver changes or oncogenic effects were observed at the doses tested under the conditions of the study. Using data from all three 2-year studies, a NOEL for fatty liver change of 6.5 mg/kg bwt/day was established.

4. A 2-year oncogenicity study in mice using dietary concentrations of 0, 50, 170, and 600 ppm (equivalent to 0, 7, 24.3, and 85.7 mg/kg bwt/day) that was negative for oncogenic effects at all doses tested under the conditions of the study. At 600 ppm, an increase in fatty change of the liver was demonstrated. The NOEL for this effect was 170 ppm (24.3 mg/kg bwt/day).

5. A rabbit teratology study that was negative for teratogenic effects at all doses tested (0, 5, 10, and 35 mg/kg).

6. A rat teratology study that demonstrated hydronephrosis at 35 mg/kg (doses tested were 0, 5, 13, and 35 mg/kg). A second study in rats (with a postpartum evaluation) again demonstrated hydronephrosis at 35 mg/kg, but also indicated that the dose level of 35 mg/kg was associated with a

maternal toxic effect (decreased body weight gain during treatment). The Agency considers the NOEL for hydronephrosis and for maternal toxicity to be 13 mg/kg.

7. A multigeneration reproduction study in rats that demonstrated decreased fertility in males and delayed parturition and dystocia in females at 5 mg/kg bwt/day. The NOEL for reproductive effects in this study was 2.5 mg/kg bwt/day.

8. Multigeneration reproduction studies in guinea pigs and mice that were negative for reproductive effects at doses up to 35 mg/kg bwt/day (highest dose tested) and 20 mg/kg bwt/day, respectively.

9. An aromatase inhibition study in rats that showed fenarimol to be a moderately weak inhibitor of aromatase activity.

The adverse reproductive effects observed in the rat multigeneration reproduction study are considered to be a species-specific effect caused by aromatase inhibition. This enzyme promotes normal sexual behavior in rats and mice, but not in guinea pigs, primates, or man. A NOEL of 35 mg/kg bwt/day for reproductive effects relevant to humans was established in the multigeneration reproduction study in guinea pigs.

10. A mouse lymphoma forward mutation assay, a DNA repair synthesis study in rat liver culture systems, gene mutation assays in *Salmonella typhimurium* (Ames test) and *Escherichia coli*, a dominant-lethal assay in Wistar rats, an assay for transformation activity in the C3H/10T 1/2 embryonic mouse fibroblast, and an *in vivo* assay for chromosome aberration in the Chinese hamster. Fenarimol did not demonstrate mutagenic activity in any of these studies. Furthermore, fenarimol did not induce altered foci or neoplastic nodules in an initiation and promotion study in rat liver tissue.

Based on the above findings, the Agency concluded that fenarimol was not oncogenic in long-term studies in rats and mice under the test conditions in which the highest dose tested for both species approached a maximum-tolerated dose as evidenced by increased fatty change in the liver.

The acceptable daily intake (ADI) based on the 2-year rat chronic feeding study (NOEL of 6.5 mg/kg bwt/day) with an uncertainty factor of 100 is calculated to be 0.065 mg/kg bwt/day. The theoretical maximum residue contribution (TMRC) from previously established tolerances and the tolerance established here is 0.000431 mg/kg/day for the general population and utilizes 0.66% of the ADI. The percentage of the

ADI for the most highly exposed subgroup, non-nursing infants (less than 1 year old), is 2.68%. The TMRC was calculated based on the assumption that fenarimol occurs at the maximum legal limit in all of the dietary commodities for which tolerances are proposed. Even with this probable large overestimate of exposure/risk, the TMRC is well below the ADI for the population as a whole and for each of the 22 subgroups considered. Thus, the dietary risk from exposure to fenarimol appears to be minimal.

The nature of the residues is adequately understood, and adequate analytical methodology is available for enforcement. Prior to their publication in the Pesticide Analytical Manual, Vol. II, the enforcement methodology is being made available in the interim to anyone who is interested in pesticide enforcement when requested from: Calvin Furlow, Public Information Branch, Field Operations Division (7505C), Office of Pesticide Programs, Environmental Protection Agency, 401 M St., SW., Washington, DC 20460. Office location and telephone number: Rm 1128C, CM 2, 1921 Jefferson Davis Hwy, Arlington, VA 22202, (703)-305-5232.

The pesticide is considered useful for the purpose for which the tolerance is sought. Based on the information and data considered, the Agency has determined that the tolerance established by amending 40 CFR part 180 will protect the public health. Therefore, the tolerances are established as set forth below. By way of public reminder, this notice also reiterates the registrant's responsibility under section 6(a)(2) of FIFRA, to submit additional factual information regarding adverse effects on the environment and to human health by these pesticides.

Any person who has registered or submitted an application for registration of a pesticide, under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) as amended, which contains any of the ingredients listed herein, may request within 30 days after publication of this document in the **Federal Register** that this rulemaking proposal be referred to an Advisory Committee in accordance with section 408(e) of the FFDCA.

Interested persons are invited to submit written comments on the proposed regulation. Comments must bear a notation indicating the document control number, [PP 3E4249/P613]. All written comments filed in response to this petition will be available in the Public Response and Program Resources Branch, at the address given above from