

thyme herb (e.g., *Thymus vulgaris*, *T. zygis*). Thyme herb is used as a food seasoning ingredient, and is generally recognized as a safe (GRAS) natural seasoning by the Food and Drug Administration (FDA) (21 CFR 182.10). Thyme oil also is recognized as a GRAS essential oil by FDA (21 CFR 182.20).

In September of 1993, the EPA issued a Reregistration Eligibility Decision (RED) for thymol. At that time the Agency concluded that thymol is an active ingredient that should be considered for a broad waiver of generic data requirements. This conclusion was based on the following information:

Thymol is a component of many non-pesticidal consumer products currently marketed in the United States. Thymol is listed as a food additive by the Food and Drug Administration (21 CFR 172.515; synthetic flavoring substances and adjuvants). Thymol is rapidly degraded in the environment to elemental constituents by normal biological, physical, and/or chemical processes that can be reasonably expected to exist where the pesticide is applied.... The phenols of thymol are considered GRAS as set forth in 21 CFR 172.515 (synthetic flavoring substances and adjuvants)....

Thymol toxicity data reported available literature cite acute oral LD<sub>50</sub> values as 980 milligrams/kilogram (mg/kg) and 880 mg/kg for the rat and guinea pig, respectively (Sax, 1984). The acute oral toxicity reported for the rat and guinea pig, respectively corresponds to Toxicity Category III. The Material Safety Data Sheet (MSDS) for the manufacture of technical grade thymol cites human health effects as irritating when exposed by inhalation, dermal or eye contact. The MSDS also estimates a human ingestion LD<sub>50</sub> at 2 grams of the synthetic thymol. Based upon an estimated thymol dermal toxicity LD<sub>50</sub> of greater than 2,000 mg/kg, the dermal toxicity would be Toxicity Category III. (Refer to pages 6 and 7 of the RED)

A summary of the submitted information on thymol toxicity allows for the statements that the acute oral LD<sub>50</sub> in the rat is 980 mg/kg and in the mouse is 640 to 1,800 mg/kg. Thymol is corrosive to the rabbit eye and skin, and is not reported as a dermal sensitizer in the guinea pig. Thymol is readily absorbed from the gastrointestinal tract and is essentially excreted in the urine as a glucuronate and sulfate conjugate of the parent compound. Dosing of rats with thymol in the feed at 667 mg/kg body weight/day (highest dose tested) for 19 weeks did not produce any harmful effects. Thymol is not mutagenic in *Salmonella*, but gives statistically significant positive results

in an Unscheduled DNA synthesis and Sister Chromatid Exchange tests, and in a cell transformation test with Syrian hamster embryonic cells. Multiple malformations are noted when thymol is injected into the air bubble or yolk sac of embryonic chickens.

#### *B. Exposure Assessment*

In examining aggregate exposure, FFDCA section 408 directs EPA to consider available information concerning exposures from the pesticide residue in food and all other non-occupational exposures, including drinking water from ground water or surface water and exposure through pesticide use in gardens, lawns, or buildings (residential and other indoor uses).

1. *Dietary exposure*—i. *Food*. Thymol is found naturally occurring in thyme herb (e.g., *Thymus vulgaris*, *T. zygis*). Thyme herb is used as a food seasoning ingredient, and is generally recognized as a safe (GRAS) natural seasoning by FDA (21 CFR 182.10). Thyme oil also is recognized as a GRAS essential oil by FDA (21 CFR 182.20). The volatile oil component of thyme herb is about 2% to 5% content, and thyme oil is reported to contain from 30% to 75% thymol, and even up to 90%. Thymol may be safely used in foods as a synthetic flavoring substance when used in the minimum quantity to produce the intended effect (21 CFR 172.515). Levels of thymol reported in foods where it is permitted as a direct food additive have been stated as 44 ppm in ice cream, ices, etc.; 2.5 ppm to 11 ppm in non-alcoholic beverages; 9.4 ppm in candy, 5 ppm to 6.5 ppm in baked goods, and 100 ppm in chewing gum. Thymol is a natural component of lime blossom honey, where the maximum thymol content has been determined to be 0.16 mg/kg.

Studies in Europe showed that when ApiLife Var was used for 8 weeks in the autumn over 1 to 5 years the maximum thymol residue observed was 0.48 mg/kg. The average (median) residue value for thymol was 0.16 mg/kg in honey. When export and import tonnage values of honey are taken into consideration with U.S. honey production, the average yearly per capita intake of honey is about 2 pounds, roughly equivalent to 1 kg. If all the honey contained 0.5 mg/kg thymol then the per capita intake of thymol would be about 1.4 µg/day. For a 60 kg adult the chronic exposure value is about 0.022 µg/kg body weight/day. If a 60 kg adult consumed 1 kg of honey containing 0.5 mg thymol in 90 days the subchronic dietary exposure to thymol would be about 2 µg/kg body weight/day. Even if all 2 kg of the thymol-

containing honey were consumed in one sitting, the acute exposure to thymol still would be as low as 83 µg.

2. *Drinking water exposure*. No drinking water exposure is expected from the pesticidal use of thymol which is confined to placement in beehives. Thymol is currently registered for use on ornamental plants, shrubs and grasses so there is some potential for exposure to water. However, thymol is a constituent of a mixture of organic compounds known to be rapidly degraded in the environment to elemental compounds by normal biological, physical and/or chemical processes. In the RED, the Agency concluded that the registered uses of thymol will result in negligible exposure of the environment and nontarget organisms (refer to page 7 of the RED). Therefore, thymol is not expected to be found in drinking water.

3. *Other non-occupational exposure*. The potential for non-dietary exposure to thymol residues for the general population, including infants and children, is unlikely because the proposed use site is limited to beehives. Thymol is a normal constituent of the human diet, as a component of thyme and thyme oil, and as a direct food additive. Therefore, while there exists a great likelihood of prior exposure for most, if not all individuals to thymol, any increased exposure due to the proposed use would be negligible. Thyme, which contains thymol, is a pesticide active ingredient for the control of aphids on ornamental plants. Thyme and thyme oil are considered minimum risk pesticides, and are exempted as active ingredients under FIFRA [40 CFR 152.25(g)].

4. *Cumulative exposure to substances with a common mechanism of toxicity*. Section 408(b)(2)(D)(v) of the FFDCA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity."

EPA does not have, at this time, available data to determine whether thymol has a common mechanism of toxicity with other substances or how to include this pesticide in a cumulative risk assessment. Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, thymol does not appear to produce a toxic metabolite produced by other substances. For the purposes of this exemption from the requirement of a tolerance, therefore, EPA has not