7. A 2-year rat chronic feeding/carcinogenicity study with no compound-related carcinogenic effects under the conditions of the study at dietary levels up to 1,250 ppm. The NOEL is 13 mg/kg bwt/day (250 ppm). The lowest-observed-effect level (LOEL) is 63 mg/kg/day based upon slight increases in liver weight to body weight ratios and periacinar vacuolation of hepatocytes.

8. A 2-year mouse oncogenic study with no compound-related carcinogenic effects under the conditions of the study at dietary levels up to 190 mg/kg/day.

Because of concerns raised over some equivocal increases in tumor incidences in the male mouse liver and the male rat adrenal medulla, and the female rat thyroid, the two chronic feeding studies were submitted to the Environmental Pathology Laboratories (EPL) for an independent reading of the microscopic slides. The new pathological evaluation by EPL and the original reports of the rat and mouse oncogenicity studies were then both submitted for review to EPA's Carcinogen Assessment Group (CAG). A final review of the carcinogenicity studies and related material was performed by the Peer Review Committee of the Toxicology Branch (TB) of the Office of Pesticide Programs (OPP).

The four major issues evaluated by CAG and the peer review group included: (1) Perifollicular cell adenomas in the thyroid of female rats; (2) adrenal medullary tumors (pheochromocytomas) in male rats; (3) liver tumors in male mice; and (4) whether the HDT (1,250 ppm) in the rat and mouse oncogenicity studies represented a maximum-tolerated dose (MTD).

Regarding the thyroid tumors in female rats, the peer review group concluded that the increased incidences of thyroid tumors in females of treated groups were not compound related. This conclusion was based on the following: (1) There was no progression of benign tumors (adenomas) to malignancy (carcinomas); (2) there was no increase in hyperplastic changes; (3) there was no dose-response relationship; and (4) the two reevaluations of the microscopic slides by the pathologists at EPL and TB in OPP further did not confirm any apparent effects observed in the original report.

The issue of a possible treatment-related increase of adrenal medullary gland tumors, namely, pheochromocytomas, in the male rat was also reassessed by both CAG and the Peer Review Committee. Both concluded that the data, especially in view of the reevaluation of the microscopic slides performed by EPL, did not support a compound-related increase of adrenal medullary tumors; the incidence of pheochromocytomas more accurately represented spontaneous variations of a commonly occurring tumor in the aged rat.

The analysis of the significance of the equivocal increase in the incidence of liver tumors in male mice was very similar to that performed for the rat thyroid and adrenal gland tumors. The original pathological reading of the tissue slides reported an elevated increase of tumors in some treatment groups; however, these increases were not evident after a reevaluation of themicroscopic slides was performed by an independent pathologist at EPL and by the reading of a CAG pathologist. The Peer Review Committee concurred that the reevaluation of the slides is reliable and does not show any compound-related increase in the incidence ofliver tumors in the mouse.

The Agency believes that the data from the rat and mouse long-term studies are sufficient to support the conclusion that metalaxyl does not show a carcinogenic potential in laboratory animals. This conclusion is supported by the following: (1) The doses tested in both the rat and mouse long-term studies approached an MTD based upon compound-related changes in liver weight and/or liver histology; (2) extensive available mutagenic evidence indicates no potential genotoxic activity which correlates with the negative carcinogenic potential demonstrated in long-term testing; (3) metalaxyl is not structurally related to known carcinogens; and (4) under the conditions of the rat and mouse tests, no indication of compound-related carcinogenic effects was noted at any of the treatment doses, sexes, or species.

The reference dose (RfD), anticipated residue contribution (ARC), and food additive regulations are covered by existing tolerances.

The nature of the residue is adequately understood. The enforcement methodology has been submitted to the Food and Drug Administration for publication in the Pesticide Analytical Manual, Volume II (PAM II). Because of the long lead time for publication of the method in PAM II, the analytical methodology is being made available in the interim to anyone interested in pesticide enforcement when requested from: Calvin Furlow, Public Response and Program Resources Branch, Field Operations Division (7506C), Office of Pesticide Programs, Environmental Protection Agency, 401 M St., SW., Washington, DC 20460. Office location and telephone number: Rm. 1132, CM #2, 1921 Jefferson Davis Highway, Arlington, VA 22202, (703)-305-5232.

There are presently no actions pending against the continued registration of this chemical.

Based on the information and data considered, the Agency has determined that the tolerances established by amending 40 CFR part 180 will protect the public health. Therefore, the tolerances are established as set forth below.

Any person adversely affected by this regulation may, within 30 days after publication of this document in the Federal Register, file written objections to the regulation and may also request a hearing on those objections. Objections and hearing requests must be filed with the Hearing Clerk, at the address given above (40 CFR 178.20). A copy of the objections and/or hearing requests filed with the Hearing Clerk should be submitted to the OPP docket for this rulemaking. The objections submitted must specify the provisions of the regulation deemed objectionable and the grounds for the objections (40 CFR 178.25). Each objection must be accompanied by the fee prescribed by 40 CFR 180.33(i). If a hearing is requested, the objections must include a statement of the factual issue(s) on which a hearing is requested, the requestor's contentions on such issues, and a summary of any evidence relied upon by the objector (40 CFR 178.27). A request for a hearing will be granted if the Administrator determines that the material submitted shows the following: There is genuine and substantial issue of fact; there is a reasonable possibility that available evidence identified by the requestor would, if established, resolve one or more of such issues in favor of the requestor, taking into account uncontested claims or facts to the contrary; and resolution of the factual issue(s) in the manner sought by the requestor would be adequate to justify the action requested (40 CFR 178.32).

EPA has established a record for this rulemaking under docket number [PP 2F4063/R2183] (including comments and data submitted electronically as described below). A public version of this record, including printed, paper versions of electronic comments, which does not include any information claimed as (CBI), is available for inspection from 8 a.m. to 4:30 p.m., Monday through Friday, except legal holidays. The public record is located in Rm. 1132 of the Public Response and Program Resources Branch, Field Operations Division (7506C), Office of Pesticide Programs, Environmental Protection Agency, Crystal Mall #2,