

T.W. Alexander Drive, Research Triangle Park, NC 27709 proposing, pursuant to section 408(d) of the Federal Food, Drug, and Cosmetic Act (FFDCA), 21 U.S.C. 346a(d), to amend 40 CFR part 180 by establishing a tolerance for residues of methyl 2-[[[(4,6-dimethoxy-2-pyrimidinyl) amino]carbonyl]amino]sulfonyl]-4-[[[(methylsulfonyl) amino]methyl]benzoate, CAS No. 208465-21-8 (Mesosulfuron-methyl, Company Code AE F130060) in or on the raw agricultural commodities wheat grain at 0.03, wheat forage at 0.60, wheat straw at 0.30, wheat hay at 0.06, wheat germ at 0.10, aspirated grain fractions at 0.25, and milled byproducts at 0.03 parts per million (ppm). EPA has determined that the petition contains data or information regarding the elements set forth in section 408(d)(2) of the FFDCA; however, EPA has not fully evaluated the sufficiency of the submitted data at this time or whether the data support granting of the petition. Additional data may be needed before EPA rules on the petition.

#### A. Residue Chemistry

1. *Plant metabolism.* The metabolism of mesosulfuron-methyl in wheat has been investigated and is understood. Identification of the extractable residues in grain was not possible due to the extremely low residue levels. In mature straw, three metabolites were identified at very low levels in addition to the parent AE F130060. Demethylation of one methoxy group on the pyrimidyl ring led to methyl 2-[3-(4-hydroxy-6-methoxy-pyrimidin-2-yl)ureidosulfonyl]-4-methanesulfonamidomethylbenzoate. Cleavage of the sulfonylurea bridge formed the interim phenyl metabolite, methyl-4-methanesulfonamidomethyl-2-sulfamoyl-benzoate, which further cyclised to 6-methanesulfonamidomethyl-1,2-benzisothiazol-3(2H)-one 1,1-dioxide. The same metabolites were also detected in green plants (forage stage) as the main components; however, the parent substance contributed to a higher proportion to the total radioactive residue. All metabolites detected in plants were also found in animal metabolism studies.

2. *Analytical method.* Based on the results of the metabolism studies, the analytical target selected was the parent compound mesosulfuron-methyl (AE F130060). Extractable residues of AE F130060 are extracted from the crop matrix by blending with a solution of acetonitrile, water and triethylamine. After filtration, the extract is partitioned with hexane, then concentrated to a reduced volume. The resulting solution

is diluted with 0.01M formic acid, and partitioned with ethyl acetate. An aliquot of ethyl acetate is evaporated to dryness and reconstituted in acetonitrile/water. This acetonitrile/water extract is analyzed by HPLC-MS/MS for AE F130060. For some forage samples, an additional solid phase extraction clean up was required to suppress matrix enhancement effects.

3. *Magnitude of residues.* The metabolism studies with <sup>14</sup>C-labelled mesosulfuron-methyl in wheat demonstrated that in general, low residues were detected in the plant samples. These results have been confirmed in a total of 24 North American residue field trials using a water dispersible granule (WG) formulation containing 75% weight/weight (w/w) mesosulfuron-methyl. The preparation was applied in a single application, at a rate of 25 g a.i./ha. Pre-harvest intervals were between 4 and 68 days, 21 and 96 days, 50 and 91 or 50 and 134 days respectively for forage, hay, straw and grain. Residues in forage and straw ranged from below the limit of quantitation (LOQ), (0.05 milligrams/kilogram (mg/kg)) to 0.55 mg/kg and 0.25 mg/kg respectively. No residues above the LOQ of 0.05 mg/kg were observed in hay. Residues in grain ranged from below the LOQ (0.01 mg/kg) to 0.026 mg/kg. Tolerances for mesosulfuron-methyl are proposed at 0.6 mg/kg, 0.06 mg/kg, 0.3 mg/kg and 0.03 mg/kg respectively, for wheat forage, hay, straw and grain. In a wheat processing study, residues of mesosulfuron-methyl in the grain reached 0.011 mg/kg following treatment of the wheat at 75 g a.i./ha. This exaggerated rate is approximately 5 times the maximum proposed label rate. In the processed fractions, residues of mesosulfuron-methyl were 0.014 mg/kg, 0.045 mg/kg and 0.014 mg/kg respectively in shorts, wheat germ and bran. No mesosulfuron-methyl residues above the LOQ (0.01 mg/kg) were observed in flour or middlings. Concentration factors of 1.3, 4.2 and 1.3, respectively were estimated for shorts, wheat germ and bran. Therefore, tolerances are proposed at 0.1 mg/kg for wheat germ and 0.03 mg/kg for milled by-products (shorts, middlings and bran). No tolerance is proposed for flour since there was no evidence of concentration. Therefore, the tolerance for wheat grain will cover flour. In the same study, samples of aspirated grain dust were collected and found to contain residues of 0.23 mg/kg. Accordingly, a tolerance of 0.25 mg/kg is proposed for aspirated grain fractions. Although, wheat grain is fed to poultry,

and cattle may be grazed on forage or fed grain, hay or straw, tolerances in meat, milk or eggs are not necessary because dietary burden calculations have demonstrated that quantifiable residues of mesosulfuron-methyl will not occur in animal tissues.

#### B. Toxicological Profile

1. *Acute toxicity.* Mesosulfuron-methyl has very low acute toxicity to mammals by all tested routes of exposure. Both the oral and dermal LD<sub>50</sub>'s in the rat are greater than 5,000 milligrams/kilogram body weight (mg/kg bwt). The acute inhalation LC<sub>50</sub> (4-hour) is greater than 1.33 milligrams per liter (mg/L) air, the maximum attainable concentration. Mesosulfuron-methyl was not irritating to rabbit skin and only slightly irritating to the eye. Mesosulfuron-methyl did not induce delayed contact hypersensitivity (skin sensitization) in the maximization test. Based on these results, mesosulfuron-methyl is expected to be in EPA Category III or IV for all routes of acute exposure.

2. *Genotoxicity.* Testing for possible genotoxic properties of mesosulfuron-methyl *in vivo* and *in vitro* gave consistently negative results. The *in vitro* test battery included investigations for gene mutation in bacteria and mammalian cells, examination of chromosomal aberrations in Chinese hamster cells and testing for unscheduled DNA-synthesis (UDS) in primary rat hepatocytes. The *in vivo* mouse micronucleus assay was also conducted. As all five tests were negative and no evidence for carcinogenicity was seen in life-time experiments in two species, results indicate that mesosulfuron-methyl does not possess significant genotoxic activity.

3. *Reproductive and developmental toxicity.* A two-generation reproduction study in rats was conducted with dietary dose levels of 0, 160, 1,600 and 16,000 ppm of technical mesosulfuron-methyl. There were no treatment-related adverse effects of the test material in any groups up to and including 16,000 ppm in the P and F1 generation male or female rats. This included mortality, clinical observations, general behavior, body weights, body weight gain, feed consumption, estrus cycle, sperm production, fertility, parturition, lactation, organ weights or microscopic findings. Therefore, the no observed adverse effect level (NOAEL) for the F0 and F1 parental animals for toxicity and reproductive effects is 16,000 ppm. The NOAEL for toxicity, growth and development of the F1a, F1b, F2a, and F2b offspring is 16,000 ppm, equivalent