

EXHIBIT 12

United States
Environmental Protection
Agency

Office of
Pesticides and Toxic Substances
Washington DC 20460

June 1986

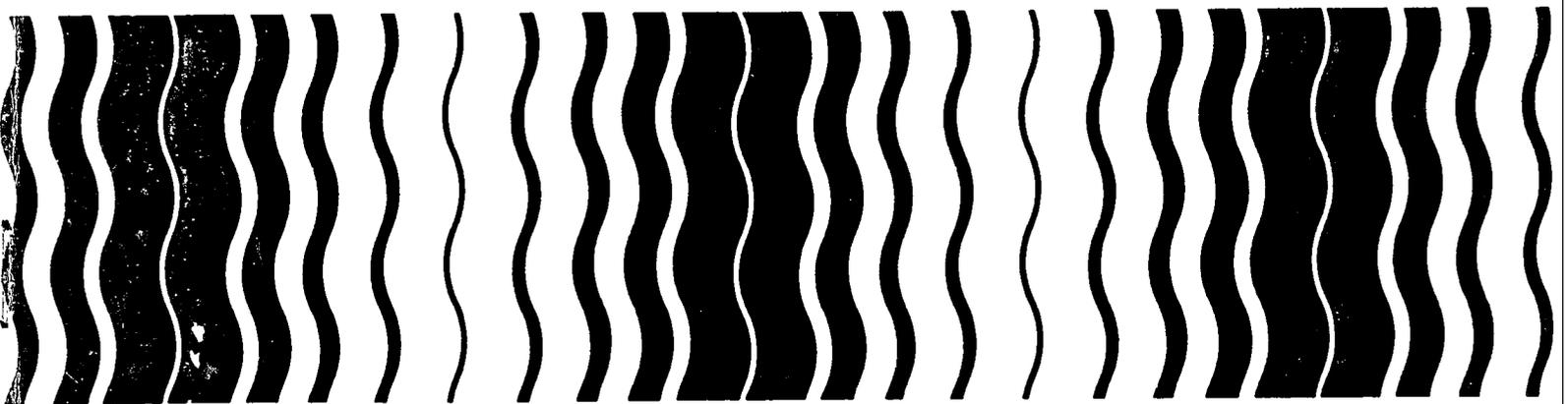


Pesticides

MAC REGISTRATION FILE ROOM

Guidance for the Reregistration of Pesticide Products Containing Glyphosate

as the Active Ingredient



These studies are not adequate to fulfill Guideline requirements (§158.135 85-1), therefore repeat studies are required.

N-Nitroso-Glyphosate

The Agency has determined that technical glyphosate contains N-nitroso-glyphosate (NNG) as a contaminant at levels of 0.1 ppm or less. The Agency has determined that oncogenicity testing of nitroso contaminants will normally be required only in those cases in which the level of nitroso compounds exceeds 1.0 ppm (see "Pesticide Contaminated with N-nitroso Compounds, proposed policy 45 FR 42854 (June 25, 1980)"). Therefore, although a chronic feeding study in rats was reviewed and found unacceptable, no additional studies are requested at this time.

Acute oral toxicity data for NNG place it in Toxicity Category III. Other acute toxicity data for NNG are not available.

Chronic toxicity studies on NNG in the dog and rat were conducted at IBT. After a raw data audit, both studies were judged to be "supplementary" (not adequate to fulfill guideline requirements). Both studies were then evaluated for scientific acceptability, and the rat study was invalid due to dosing of the control groups with an excessive amount of NaCl which resulted in high mortality of control animals. The dog study remained classified "supplementary" due to the lack of supporting raw data as identified in the raw data audit validation report. The only apparent treatment-related findings in the dog study were an increase in absolute and relative kidney weights and in blood glucose in high-dose (30 mg/kg/day) females. The NOEL for this apparent effect was 10 mg/kg/day.

A 90-day subchronic oral toxicity study with NNG was conducted in the rat. The principal effect of treatment was a dose-related decrease in survival, food consumption, and body weight gain. A NOEL was not established in this study since these effects were noted at the lowest dose tested, 3000 mg/kg/day. The study was classified as "supplementary" data due to inadequate reporting of clinical signs and necropsy data, and inadequate identification of the test material.

A rat metabolism study conducted with NNG demonstrated that NNG is rapidly absorbed and excreted, with the kidneys the preferential route of elimination. These findings are in direct contrast with the results of the metabolism studies with glyphosate, which found that absorption from the gut

was poor and the majority of excretion occurred in the feces due to unabsorbed radiolabel. Tissue residues after five consecutive doses were minimal, as no tissue contained more than 1.5 ppm of radiolabel.

No acceptable studies for mutagenic or reproductive effects are available at present for NNG.

Because the amount of N-nitroglyphosate is less than 1.0 ppm no additional toxicology data are required; therefore, none of the above studies are to be repeated or required.

Plant Metabolite--Aminomethylphosphonic Acid

The Agency has determined that the metabolite aminomethylphosphonic acid (AMPA) is formed on plants in amounts that can range as high as 28 percent of the total residue on the plant. Since the extent of glyphosate metabolism was not adequately addressed in the rat metabolism study, the possibility exists that the AMPA metabolite could pose a hazard to humans that was not evaluated by testing the parent compound glyphosate. If an acceptable rat metabolism study is submitted which demonstrates significant conversion of glyphosate to AMPA in animals, additional studies on this metabolite may be not necessary, since the toxicity of AMPA will have been assessed by chronic feeding studies with the parent compound glyphosate.

Acute oral toxicity and primary skin irritation data place AMPA in Toxicity Category IV. The primary eye irritation study demonstrated that AMPA was slightly irritating to the eye, corresponding to Toxicity Category III.

A 90-day subchronic feeding study was submitted that demonstrated irritation of the urinary bladder in rats treated with 1200 mg/kg/day, the lowest effect level (LEL) ; in this study. This irritation was manifested in the form of hyperplasia of the cells lining the bladder, and was noted with increased incidence and severity at the highest dose tested, 4800 mg/kg/day. Epithelial hyperplasia of the renal pelvis was also noted in high-dose rats. The NOEL for this effect was 400 mg/kg/day, and the study was classified as Core-Minimum.

A rat metabolism study demonstrated that AMPA is rapidly excreted as the parent compound. No evidence for bioaccumulation was noted in this study, which was classified as Supplementary data because the number of animals studied was not reported, only males were studied, and the effects of a minimally toxic dose and repeated nontoxic doses on excretion, metabolism, and accumulation were not assessed.