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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: HED Cover Memo for the Chlorpropham Registration Standard

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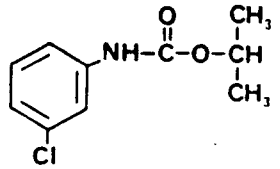
Introduction

Chlorpropham (1-methylethyl 3-chlorocarbanilate) is an herbicide registered for use on alfalfa, beans, blackberries, blueberries, carrots, clover, cranberries, garlic, onions, potatoes, raspberries, safflower, soybeans, spinach, sugar beets, tomatoes, trefoil, perennial grasses (seed crop), tobacco, and ornamental plants and forest trees. Aerial applications are permitted on alfalfa, soybeans, sugar beets and tomatoes. The chemical structure of chlorpropham is:



The available data base for chlorpropham is poor with extensive data gaps in all areas (toxicology, residue chemistry, ecological effects, and environmental fate). Acceptable risk criteria for restricted use and endangered species were theoretically exceeded for avian and aquatic species. However, it is recommended that no regulatory action be taken until sufficient data are available to permit a more reliable risk assessment. Although insufficient data are available to reliably assess the leaching potential of chlorpropham, its high solubility and relative stability in water in addition to the known mobility of a related chemical, propham, indicate that leaching and contamination of groundwater are likely to occur.

HED is concerned by a published report of 3-chloroaniline in several plant species following treatment with chlorpropham (James and Prendeville. 1969. J. Agric. Food Chem. 17(6):1257). Several published positive mutagenicity studies exist for the chloranilines, particularly 4-chloroaniline, indicating their potential for inducing carcinogenic effects. In addition, a published

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NTP carcinogenicity bioassay study (Goodman et al. 1984. J. National Cancer Institute 73:265) showed dose-dependent incidences of splenic sarcomas and fibrosis in rats fed 4-chloroaniline. Therefore, the Registrant is required to conduct analyses specifically for 3-chloroaniline, in addition to other known residues of concern, in all required residue trials on food crops and livestock. Depending on the results of these residue trials, toxicity testing on the 3-chloroaniline metabolite may be necessary.

Product Chemistry

The sole manufacturing use products are two 98% technical products registered by Aceto Agricultural Chemicals Corp. (EPA Reg. Nos. 2749-102 and 2749-117). Although product chemistry data may have been submitted in the past, the Agency has determined that these data must be resubmitted for each pesticide. New requirements have been introduced, and previously submitted data must be updated.

Residue Chemistry

1. Metabolism: The metabolism of chlorpropham in growing plants has been adequately described. The herbicide may be translocated from roots into shoots and residues include chlorpropham, isopropyl 3-chloro-6-hydroxycarbanilate, isopropyl 3-chloro-4-hydroxycarbanilate, 1-hydroxy-2-propyl-3-chlorocarbanilate (isopropyl-OH-CIPC), isopropyl 3-chloro-2-hydroxycarbanilate, and 3-chloroaniline. Also, FDA has reported the presence of p-methoxychlorpropham in potato tubers following postharvest treatment and in market basket samples of processed potato products. Additional data are required regarding the metabolism of chlorpropham in stored potato tubers treated postharvest and in livestock (ruminants and poultry). Although the available metabolism data for dairy animals are inadequate, the following metabolites have been identified in milk: isopropyl 3-chloro-4-hydroxycarbanilate and 3-chloro-4-hydroxyacetanilide. Tolerances for residues of chlorpropham in or on potatoes and soybeans are currently expressed in terms of chlorpropham and isopropyl-OH-CIPC, calculated as chlorpropham (40 CFR 180.181). Interim tolerances for residues in or on all remaining plant commodities and in animal commodities (eggs, milk, and the meat, fat, and meat by-products of cattle, goats, hogs, horses, poultry and sheep) are currently expressed in terms of chlorpropham per se (40 CFR 180.319). The tolerance definition will be reassessed on receipt of the required metabolism data.

2. Analytical Enforcement Methods: Chlorpropham per se is adequately recovered by FDA multiresidue protocol I published by NTIS under order No. PB203734/AS. Protocols II, III and IV must be tested using chlorpropham per se and isopropyl-OH-CIPC must be tested using all four protocols. These protocols plus all data collection methods the Registrant has used or will use in the future must be tested in conjunction with the required metabolism studies so that their ability to release all bound and conjugated residues of concern can be assessed.

3. Storage Stability Data: Chlorpropham and isopropyl-OH-CIPC are stable in frozen plant commodities for up to 21 months. Storage data (storage interval and conditions) must be submitted for all previously submitted samples used to support or assess established tolerances. These data must be accompanied by data depicting the stability of residues in similar samples stored for the time intervals and under the conditions specified, with the exception of

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plant commodities stored frozen for ≤ 21 months. In addition, storage data (time interval, conditions, stability) must accompany all residue data required in the Standard.

4. Residues in Raw Agricultural and Processed Commodities, and Meat, Milk, Poultry and Eggs: The available data indicate that residues of chlorpropham in or on the following plant and animal commodities will not exceed the established tolerances published in 40 CFR 180.181 and 40 CFR 180.319: soybeans, clover forage, and cranberries. On receipt of the required metabolism, analytical method validation, and storage stability data, the Agency's conclusions regarding the adequacy of these tolerances may change. Established tolerances for residues in or on carrots and safflower are too low, but additional data are needed to determine an appropriate tolerance increase. Insufficient data are available to assess the adequacy of the established tolerances for residues in or on: potatoes, alfalfa forage, alfalfa hay, beans, blackberries, blueberries, clover hay, garlic, grass forage, grass hay, onions, raspberries, spinach, sugar beets, sugar beet tops, tomatoes, milk, eggs, and the meat, fat, and meat by-products of cattle, goats, hogs, horses, poultry and sheep. Data are also required to determine whether food/feed additive tolerances are needed for residues in the processed products of potatoes, safflower, soybeans, sugar beets and tomatoes. The Registrant must either propose tolerances for residues in or on birdsfoot trefoil forage and hay or remove this crop from all labels. The interim tolerances for residues in or on rice grain and succulent or dried peas should be revoked since no registered uses on these commodities exist.

Residue and processing studies should not be conducted until all requested metabolism and analytical method validation data have been received and reviewed by the Agency. This tiered approach may prevent unnecessary repetition of residue trials. After receipt of all required data, the interim tolerances for chlorpropham in 40 CFR 180.319 should be revoked concomitant with establishment of permanent tolerances for all residues of concern in 40 CFR 180.181.

Toxicology

1. Acute Effects and Irritation Studies: No acceptable data are available for acute oral, dermal or inhalation toxicity; primary eye or dermal irritation; or dermal sensitization. These studies are required. No delayed neurotoxicity was demonstrated in the hen at 5000 mg/kg. [This test is not required for chlorpropham because it is not an organophosphate inhibitor of cholinesterase.]

2. Subchronic Effects: No data are available for subchronic oral, dermal or inhalation toxicity, or subchronic neurotoxicity. Subchronic dermal (21-day) and subchronic oral toxicity studies in the rodent and non-rodent are required. However, the subchronic oral studies need not be submitted if adequate chronic rodent and nonrodent studies are submitted. Subchronic dermal (90-day) and inhalation toxicity studies are not required for the current use patterns. Also, since acute delayed neurotoxicity data are not required and data from mammalian toxicity studies show no evidence of neurotoxicity, no subchronic neurotoxicity study is required.

The 21-day smoke inhalation study was considered acceptable but failed to demonstrate a NOEL. Mice were exposed to smoke from standard tobacco samples spiked with chlorpropham, 2-hydroxychlorpropham and 4-hydroxychlorpropham.

Dose related increases in kidney and spleen weights occurred at all dose levels (60, 180, and 600 ppm chlorpropham). If chlorpropham residues on tobacco greater than 0.1 ppm are detected, an additional smoke inhalation study will be required.

3. Chronic Effects: Chronic toxicity studies in the rodent and nonrodent are required. However, supplementary studies in the rat and the dog suggest that chlorpropham is of low chronic toxicity. Little or no toxicity was observed at 200 and 2000 ppm dose levels but at 20,000 ppm effects included decreased body weight, depressed hematocrit and hemoglobin concentrations, and organ/body weight ratio increases for liver and spleen. The NOEL for the 1-year dog study was 2000 ppm or 40.8-54.8 mg/kg/day. No acceptable oncogenicity studies are available. Studies are required in two species. No terata occured at dose levels $\leq$ 1000 mg/kg/day in the rat or $\leq$ 500 mg/kg/day in the rabbit. Maternal toxicity NOELs were 100 mg/kg/day in the rat and 250 mg/kg/day in the rabbit; and developmental toxicity NOELs were 350 mg/kg/day in the rat and 125 mg/kg/day in the rabbit. No reproductive effects were noted at dose levels $\leq$ 10,000 ppm in the rat.

4. Mutagenicity Tests: A gene mutation study using the mouse lymphoma test system demonstrated no mutagenic effects. However, studies are required for structural chromosome aberrations and other genotoxic effects.

5. Special Studies: A rat metabolism study is required. Under present use patterns, no domestic animal safety or dermal absorption studies are required.

If the plant metabolite, p-methoxy-chlorpropham, which has been found at levels as high as 0.17 ppm in treated raw potatoes and 0.063 ppm in french fried potatoes is not found in the rat metabolism study, additional studies depicting the toxicity of this metabolite may be required (acute oral, dermal, and inhalation studies; and mutagenicity tests). In addition, if the plant and livestock metabolism and residue studies reveal metabolites which are present at significant levels (e.g., 3-chloroaniline), additional studies depicting their toxicity may also be required.

Tolerance Reassessment

Tolerances have been established for residues of chlorpropham in or on a variety of raw agricultural plant commodities, meat, milk, and eggs (40 CFR 180.181 and 40 CFR 180.319). However, due to the lack of acceptable plant and animal (livestock) metabolism data, storage stability data, and residue data, a conclusive tolerance reassessment cannot be conducted. Based on chronic effects observed in a two-generation rat reproduction study (slow weight gain; microscopic lesions in kidneys, spleen, liver and marrow; gross spleenic lesions; and organ weight changes in the liver and spleen), a Provisional Acceptable Daily Intake (PADI) has been established at 0.2 mg/kg/day based on a NOEL of 1000 ppm and an uncertainty factor of 300. [An uncertainty factor of 100 was used to account for the inter- and intraspecies difference and a factor of 3 was used to account for the inadequate data base for chronic toxicity.] The Theoretical Maximum Residue Contribution (TMRC) to the human diet was based upon published tolerances. The TMRC for 22 subgroups of the U.S. population ranged from 0.0182-0.1154 mg/kg/day which occupies 9-58% of the PADI. Upon receipt of the requested residue chemistry and toxicology data, the chlorpropham tolerances will be reassessed.

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Ecological Effects

1. Avian Studies: A supplementary study indicates that chlorpropham is practically nontoxic to waterfowl (mallard LC_{50} is greater than 2000 mg/kg). Acute oral toxicity and subacute dietary toxicity studies (upland game bird and waterfowl) are required. Avian reproduction studies may be required, depending on the results of the avian acute oral toxicity, residue monitoring and environmental fate studies.

2. Aquatic Studies: Supplementary studies indicate that chlorpropham is moderately toxic to coldwater and warmwater freshwater fishes (bluegill sunfish LC_{50} = 6.3-6.8 ppm; rainbow trout LC_{50} = 3.02-5.7 ppm). The following aquatic studies are required: acute toxicity to cold- and warmwater fish, freshwater invertebrates, and estuarine/marine species of fish, mollusks and shrimp with the technical grade of the active ingredient and a typical end-use product; and aquatic invertebrate life-cycle, fish early life stage and fish life cycle studies for both freshwater and estuarine/marine species. These studies may also be required for degradation products depending on the results of environmental fate studies. Aquatic organism accumulation studies may be required depending on the results of environmental fate and residue monitoring studies.

3. Field Testing and Monitoring: Residue monitoring studies are required for terrestrial food, terrestrial non-food, and aquatic food crop uses. These monitoring data will be used in conjunction with required toxicity data to conduct reliable ecological risk assessments. Simulated and actual field testing may also be required depending on the results of acute and chronic toxicity, residue monitoring and environmental fate studies.

4. Precautionary Statements: Manufacturing- and end-use product labels must be amended to include the following precautionary statements:

> Manufacturing-Use: "Do not discharge effluent containing this product into lakes, streams, ponds, estuaries, oceans, or public waters unless this product is specifically identified and addressed in an NPDES permit. Do not discharge effluent containing this product to sewer systems without previously notifying the sewage treatment plant authority. For guidance, contact your State Water Board or Regional Office of the EPA."
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> End-Use (Terrestrial Food and Non-Food Crop): "Do not apply directly to water or wetlands (swamps, bogs, marshes, potholes). Do not apply where runoff is likely to occur. Do not contaminate water by cleaning of equipment or disposal of wastes."
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> End-Use (Aquatic Food Crop): "Consult your State Fish and Game Agency before applying this product to public waters to determine if a permit is needed for such an application. Do not contaminate water by cleaning of equipment or disposal of wastes."

Additional precautionary labeling for avian species, aquatic invertebrates and estuarine/marine organisms may be required, depending on the results of acute toxicity studies.

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5. Restricted Use and Endangered Species Considerations: Acceptable risk criteria for restricted use and endangered species were theoretically exceeded for avian and/or aquatic species. However, these assessments were based upon an inadequate data base. It is recommended that no regulatory action be taken until required toxicity, environmental fate and residue monitoring studies have been evaluaated so that all regulatory decisions may be adequately supported.

Exposure Assessment

1. Environmental Fate: Chlorpropham is relatively stable in sterile water in the dark. After 32 days in aqueous buffered solutions at pH 4, 7, and 9 held in the dark at 40 C, about 90% of the applied chlorpropham remained undegraded. The remaining environmental fate studies were inadequate, but supplementary data indicate that chlorpropham dissipates with a half-life of < 14 days in the upper 3 inches of silty clay loam and silt loam soils regardless of site or application procedure (incorporated or surface-applied). Also, fish accumulation data indicate that chlorpropham bioaccumulated in the skinless fillet of a bluegill sunfish to 100x the levels in water. The following studies are required: photodegradation in water and on soil, aerobic and anaerobic soil metabolism, leaching and absorption/desorption, volatility (lab), field dissipation, and irrigated crop and fish accumulation. Field volatility, long-term soil dissipation, and aquatic non-target organism studies may also be required, depending on the results of other required studies.

2. Groundwater: Insufficient data are available to permit a reliable prediction of the leaching potential of chlorpropham. However, taking into account the high solubility and relative stability of chlorpropham in water and the mobility of a related chemical, propham, chlorpropham can be expected to leach and might enter groundwater. Chlorpropham was the subject of a groundwater data call-in notification (July 24, 1984) and the Registrant has been asked to respond to this DCI in a letter from J. Ackerman (RD), dated May 5, 1987.

3. Rotational Crops: Supplementary data indicate that chlorpropham accumulates in rotational crops planted 12 months after treatment. Additional rotational crop studies (confined and field) are required.

4. Reentry and Protective Clothing: Based on the available toxicological data obtained from the TOX Branch, no apparent human exposure, protective clothing or reentry data are required at this time. In addition, there are no PIMS or accident reports concerning chlorpropham.

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