United States
Environmental Protection
Agency

Office of Prevention, Pesticides
and Toxic Substances
(7501C)

Pesticide Fact Sheet

Name of Chemical: Mesotrione
Reason for Issuance: Conditional Registration
Date Issued: June 4, 2001

DESCRIPTION OF CHEMICAL

Generic Name:	[2-[4-(methylsulfonyl)-2-nitrobenzoyl]-1,3-cyclohexanedione
Common Name:	Mesotrione
Trade Names:	Callisto Herbicide
EPA Chemical Code:	122990
Chemical Abstracts Service (CAS) Number:	104206-82-8
Year of Initial Registration:	2001
Pesticide Type:	Herbicide
U.S. and Foreign Producers:	Syngenta Crop Protection, Inc. P.O. Box 18300 Greensboro, NC 27419

USE PATTERNS AND FORMULATIONS

Mesotrione will be applied pre- and post-emergence through ground or aerial application equipment. Mesotrione has herbicidal activity against broadleaf weeds. It's efficacy is the result of the inhibition of the enzyme 4-hydroxyphenylpyruvate dioxygenase (HPPD) enzyme in target plants. Following treatment, in sensitive plants carotenoid biosynthesis is disrupted in the chlorophyll pathway, resulting in a bleaching effect.

SCIENCE FINDINGS

SUMMARY

Hazard and risk assessments were conducted in relation to this registration application and tolerance petition for mesotrione on field corn that suggest that its use, consistent with the proposed labeling measures, will be protective of the public health and the environment. There are no other registrations for this chemical. Therefore, aggregate exposures to the general public are based on food plus water calculations derived from this use.

In estimating risks from this use, the Health Effects Division (HED) in EPA used conservative Tier 1 exposure assumptions. Tolerance level residues and 100 percent crop treated exposure assumptions were used in this risk analysis. An acute risk assessment was not calculated because no suitable endpoint was selected which could be attributable to a single-dose exposure.

Plasma tyrosine levels were increased in the rat, mouse and dog in the chronic and reproduction studies in which the levels were measured. The ocular, liver and kidney effects seen are believed to be mediated by the high tyrosine levels in the blood caused by inhibition of the enzyme 4-hydroxyphenylpyruvate dioxygenase (HPPD). Even though the rat is the most sensitive species to this effect compared to the dog and the mouse, EPA concludes that the mouse is a more appropriate model for assessing human risk than is the rat since the enzyme activity in the secondary degradation pathway in mice is similar to humans. The chronic dietary risk assessment was based on a Lowest Observed Adverse Effect Level (LOAEL) of 2.1 mg/kg/day in the mouse reproduction study and a safety factor of 3000. The Food Quality Protection Act (FQPA) Safety Factor Committee retained the 10x safety factor intended for the protection of infants and children because there is quantitative evidence of increased susceptibility demonstrated in the oral prenatal developmental toxicity studies in rats, mice, and rabbits. Delayed ossification was seen in the fetuses at doses below those at which maternal toxic effects were noted. Maternal toxic effects in the rat were decreased body weight gain during treatment and decreased food consumption and in the rabbit, abortions and GI effects. Thus, the Population Adjusted Dose (PAD) for chronic risk assessment is 0.0007 mg/kg/day. The chronic dietary risk assessment suggests that the requested uses will utilize 1.8% of the cPAD for the U.S. population, 4.3% of the cPAD for All Infants (< 1 year old) and 4.2% of the cPAD for Children 1-6 years old. Surface and ground water estimated environmental concentrations (EECs) were used to compare against back-calculated drinking water levels of comparison (DWLOCs) for the aggregate risk assessment. The chronic EECs are less than the DWLOCs. Thus, HED concluded that chronic aggregate exposures to mesotrione are not likely to exceed the Agency's level of concern for any population subgroup. HED did not perform a quantitative cancer risk assessment because the data suggest that no evidence of carcinogenicity was noted in the mice or rat studies.

Risks to agricultural workers were also considered. HED determined that short- and intermediate-term exposures may occur. Since mesotrione may be applied only twice per year, long-term exposures are not expected from the proposed uses. Since no more than 30 days exposure are expected for handlers, the worst case occupational risk for mixing/loading liquids for aerial application is 30 Margin of Exposure (MOE) without gloves. With the addition of gloves, all MOEs are greater than 300. Since the label required PPE is a single layer of clothing

and gloves, the MOEs for all scenarios do not exceed EPA's level of concern.

The Environmental Fate and Effects Division (EFED) in EPA has reviewed this action and concluded that mesotrione is not persistent but degradates MNBA [4-(methylsulfonyl)-2-nitrobenzoic acid] and AMBA [2-amino-4-(methylsulfonyl)benzoic acid] may be persistent under suboxic conditions such as subsoil and groundwater. Estimated environmental concentrations in water were calculated using EPA's models and factored into the human health risk assessment. Mesotrione is practically non-toxic to avian species, small mammals, and aquatic species. It is considered relatively non-toxic to bees. Non-target plants may be at risk from its use. There are no concerns for mesotrione for terrestrial or aquatic endangered animals. Syngenta is a member of the Endangered Species and Spray Drift Task Forces and any measures developed by the Task Forces to mitigate risks to non-target plants will be applied to mesotrione as well as other registered herbicides.

SCIENTIFIC FINDINGS

EPA reviewed the submitted product chemistry, toxicology, residue chemistry, occupational exposure, ecological effects and environmental fate data. A summary of these assessments follows:

Health Effects Division's Review- Hazard Identification

Mesotrione has low acute toxicity via the oral, dermal, and inhalation routes. It is a mild eye irritant, but is not a dermal irritant or a dermal sensitizer. In sub-chronic and chronic oral studies, ocular lesions, liver and kidney effects, and/or body weight decrements were the major adverse effects seen in the rat, mouse, and dog. Plasma tyrosine levels were increased in the rat, mouse and dog in the chronic and reproduction studies in which levels were measured. The ocular, liver and kidney effects are believed to be mediated by the high tyrosine levels in the blood caused by inhibition of the enzyme 4-hydroxyphenylpyruvate dioxygenase (HPPD). Even though the rat is the most sensitive species to this effect compared to the dog and the mouse, the Mechanism of Toxicity Science Assessment Review Committee (SARC) concluded that the mouse is a more appropriate model for assessing human risk than is the rat since the enzyme activity in the secondary degradation pathway in mice is similar to humans. There was no evidence of carcinogenic potential in either the rat chronic toxicity/carcinogenicity or mouse carcinogenicity studies and no concern for mutagenicity. No evidence of neurotoxicity or neuropathology was seen in the acute and subchronic neurotoxicity studies. In the multi-generation mouse reproduction study, one F_1 male and one F_1 female had retinal detachment with marked cataractous changes at the highest dose tested (>1000 mg/kg/day). In the subchronic toxicity dog study, the high-dose females had decreased absolute and relative brain weights; however, no microscopic abnormalities were noted in any brain tissue from the high-dose group and the effect was not observed in the chronic toxicity dog study. Therefore, there is some concern about the effects of elevated plasma tyrosine levels on the developing nervous system in children due to a
report by Ruetschi *et al* (2000)[1] that some patients with tyrosinemia III (an autosomal recessive

[1] Ruetschi, U., et.al., Mutations in the 4-hydroxyphenylpyruvate dioxygenase gene (HPD) in patients with tyrosinemia type III. Hum. Genet. 106(6): 654-662.

disorder in which HPPD is deficient) were presented with mental retardation or neurological symptoms. There was evidence of increased susceptibility of rats, mice and rabbits to *in utero* and/or post-natal exposure to mesotrione.

No appropriate endpoint was available to quantitate risk to the general U.S. population or to females 13-50 years old from a single-dose administration of mesotrione. Therefore, there is no acute reference dose (aRfD) or acute population adjusted dose (aPAD). The short-term incidental oral endpoint is based upon decreases in body weight gain during treatment and decreases in food consumption. The short-term dermal and inhalation endpoints are based upon delays in skeletal ossification and changes in *manus/pes* (forepaws/hindpaws) ossification assessments seen in oral developmental studies. The chronic and intermediate-term endpoints for all routes of exposure are based upon tyrosinemia in adults and pups and ocular discharge in pups observed in a mouse reproduction study. The chronic RfD is 0.007 mg/kg/day and the chronic population adjusted dose (cPAD) is 0.0007 mg/kg/day. Mesotrione is classified as "not likely to be carcinogenic to humans" based upon lack of evidence of carcinogenicity in rats and mice. Therefore, a cancer risk assessment is not required. Since oral studies were selected for all durations of dermal and inhalation exposure, a 25% dermal-absorption factor and a 100% inhalation-absorption factor (relative to oral absorption) were used in the route-to-route extrapolation.

FQPA Decision

HED recommended that the 10x safety factor to account for enhanced sensitivity of infants and children *be retained* for the general U.S. population and all population subgroups and scenarios. Consequently, the cPAD value is 0.0007 mg/kg/day. This decision was based on quantitative evidence of increased susceptibility demonstrated in the oral prenatal developmental toxicity studies in rats, mice, and rabbits and in the multi-generation reproduction study in mice. Quantitative evidence of increased susceptibility was not demonstrated in the multi-generation reproduction study in rats since no no-observed-adverse-effect-level (NOAEL) was established for parental or offspring systemic toxicity. However, there is evidence of a qualitative increase in susceptibility since the tyrosinemia observed in the young was more severe than that observed in the adults.

A chronic dietary exposure analysis was conducted using the Dietary Exposure Evaluation Model (DEEM™, ver 7.72), which utilizes consumption data from the USDA 1989-92 Nationwide Continuing Surveys of Food Intake by Individuals (CSFII). Acute and cancer dietary exposure analyses were not conducted since no acute doses or endpoints were selected for the general U.S. population (including infants and children) or the females 13-50 years old population subgroup and mesotrione was classified as not a carcinogen, respectively. The following conservative assumptions were made for the chronic dietary analysis: HED-recommended tolerance level residues for field corn, DEEM™ default processing factors for field corn commodities, and assuming all field corn is 100% treated with mesotrione. The chronic dietary food exposure estimates were less than HED's level of concern (<100% cPAD) for the general U.S. population and all population subgroups. Specifically, the most highly exposed population subgroup was "all infants (<1 year old)" at 4.3% of the cPAD.

Drinking Water

The registrant has submitted (without request from the Agency) two interim reports on a prospective groundwater monitoring (PGM) study at a site in Michigan. However, until the studies are completed and final report submitted to the Agency, these data cannot be used. Since HED does not have ground or surface water monitoring data to calculate quantitative aggregate exposure, estimates of mesotrione levels in surface and ground water were made using computer modeling. The estimated environmental concentrations (EECs) for surface water [from GENEEC (Generic Environmental Concentration) modeling] are 20 ppb and 4.3 ppb for the acute and chronic (56-day) scenarios, respectively. The EEC for ground water [from SCI-GROW (Screening Concentration in Ground Water) modeling] is 0.15 ppb to be used for both acute and chronic scenarios. All the EEC values are less than the lowest drinking water levels of concern (DWLOC) value of 6.7 ppb (specifically for the "all infants (<1 year old)", and "children 1-6 years old" sub-populations) determined for the chronic scenario, and therefore do not exceed HED's level of concern.

Consideration of Risks to Pesticide Applicators and Handlers

The proposed use of the herbicide Callisto Herbicide, a suspension concentrate formulation containing 40% of the active ingredient (a.i.), mesotrione, is for pre- and postemergence control of broadleaf weeds in field corn. Mesotrione may be applied either by ground sprayers or by aerial application up to corn height of 30" tall. A maximum of two applications per season and 0.43 lbs a.i./A/season are proposed. For preemergence application, Callisto Herbicide is proposed for use at 0.188-0.24 lbs ai/A by groundboom. In a single postemergence application, 0.094 lbs a.i./A should not be exceeded.

Based on the proposed use patterns, short-term dermal and inhalation exposures are expected for private applicators (farmers treating their own crops) and commercial applicators. Since no chemical-specific data are available to assess potential exposure to workers, the exposure and risk assessment presented in this document are based on the Pesticide Handler Exposure Database Version 1.1 (PHED, Surrogate Exposure Guide, August 1998). The maximum application rate listed on the label was used for all calculations. The standard values for acreage were taken from HED Exposure Science Advisory Committee (Expo SAC) Policy #09, effective 5-JUL-2000. Both the low and high number of acres treated per day were used to demonstrate a range of potential exposure. When wearing the label required personal protective equipment (PPE) (single layer of clothing and gloves), all Margins of Exposure (MOEs) do not exceed HED’s level of concern, with the exception of the intermediate-term mixer/loader in support of aerial application.

Currently it is HED’s draft policy that short-term endpoint durations may be increased to 30 days on a case by case basis. In the case of mesotrione, the same endpoint [rat developmental endpoint (LOAEL = 100 mg/kg/day)] is still appropriate for the 0 to 30 day exposure period since it provides protection for developmental effects seen below maternally toxic doses. For the proposed use of mesotrione, no longer than 30 days of exposure is expected for both private and commercial handlers. Using the redefined exposure durations, all MOEs for handler of mesotrione are below HED’s level of concern.

Workers having potential re-entry exposure to mesotrione from the proposed use include scouts and workers re-entering treated fields to perform irrigation tasks. Since mesotrione will be applied at the early stages of crop growth (pre- or post-emergent) and up to corn height of 30

inches, low potential for post-application exposure is expected. In order to demonstrate that minimal exposure and risk are expected, a post-application exposure assessment was done for scouts. The estimated MOE for scouting activities related to the proposed use of mesotrione on field corn do not exceed HED's level of concern

Environmental Fate and Effects Division's Review

Mesotrione is not persistent in water and soil as indicated by the photolysis, aerobic and anaerobic soil metabolism and terrestrial field dissipation studies. Mesotrione degradates are mobile, thus they have the potential to reach groundwater and/or surface water. Mobility and persistence are of the greatest concern in cold climates with low pH soils. Additional information is being required to fully characterize mesotrione's potential to contaminate ground water.

Mesotrione has been determined to be practically non-toxic to birds and small mammals, relatively non-toxic to honey bees, practically non-toxic to warm and cold water fish, and practically non-toxic to daphnids. EFED's judgement is that mesotrione is unlikely to present a risk to aquatic and terrestrial animals on an acute or chronic basis for the tested species. Loss of habitat and food items may indirectly affect terrestrial and aquatic organisms as a result of damage to non-target plants from off-target transport. There is a concern for non-target terrestrial and aquatic plants form the proposed use. Non-target plants may be exposed to mesotrione by spray drift, blowing dust particles, and runoff and reuse of surface an groundwater for irrigation. Additional data is being required to fully characterize the risk to non-target plants. Labeling statements will advise users about the risks to non-target plants. Syngenta is a member of the Endangered Species and Spray Drift Task Forces which are addressing the issue of toxicity to non-target organisms.

OUTSTANDING DATA

The following details the data gaps and/or additional information required from the registrant:

Chemistry

Adequate storage stability data in the plant and livestock metabolism studies.
Revised interference study.

Toxicology

Developmental Neurotoxicity Study (DNT) in the mouse .
28-day Inhalation Study.

Environmental Fate and Effects

Phytotoxicity studies
Improvement in the extraction method in the soil analytical method
Prospective Groundwater Study in the Southern USA

PUBLIC INTEREST FINDING:

Callisto Herbicide is an effective in controlling broadleaf weeds in field corn. It will replace atrazine and isoxaflutole herbicides. Mesotrione is a new class of herbicide and if used in Resistance Management Programs it can mitigate the increase in resistant biotypes. There is no evidence of carcinogenicity in the mice or rat studies conducted with mesotrione.

GOVERNMENT PERFORMANCE AND RESULTS ACT (GPRA)

Registering mesotrione will meet the objectives of GPRA title 3.1.1 by assuring new pesticides that enter the market are safe for humans and the environment and title 4.1.2 by reducing environmental exposure to herbicides.

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