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Office of Prevention, Pesticides
and
Toxic Substances

DATE: June 14, 2007

TXR# 0054620

MEMORANDUM

SUBJECT: CHLORSULFURON: Waiver Requests: 21-Day Dermal Toxicity Study (DB Barcode D313364) and Subchronic Inhalation Toxicity Study (DB Barcode D313365).

FROM: Linda L. Taylor, Ph.D.
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THRU: Michael Metzger, Branch Chief
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TO: Susan Jennings
Special Review and Reregistration Division (7508P)

PC Code: 118601

I. CONCLUSIONS: The data requirements for a 21-day repeat dermal toxicity study and a subchronic inhalation toxicity study for chlorsulfuron are waived, based on the justification/rationale provided by DuPont. **Dermal** study: With the current oral endpoint used in the dermal risk assessments, the dermal Margins-of-Exposure far exceed the target MOE value of 300. **Inhalation** study: Chlorsulfuron is Toxicity Category IV for inhalation exposure and an extrapolated MOE is greater than 3000, which satisfies Waiver Category 4 of the Waiver Criteria for Multiple-Exposure Inhalation Toxicity Studies guidance.

II. ACTION REQUESTED: Please address the waiver of the 21-day repeat dermal toxicity study and the waiver of the subchronic inhalation toxicity study for chlorsulfuron, as submitted by DuPont.

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The registrant [DuPont] has submitted waiver requests and justification/rationale for the 21-day repeat dermal toxicity study and the subchronic inhalation toxicity for chlorsulfuron. DuPont believes that the potential risks associated with the use of chlorsulfuron can be assessed without conducting these additional studies and is requesting that both be waived on the basis of existing data and/or the low toxicity and low exposure potential for chlorsulfuron.

Arguments put forth by DuPont include the following:

DERMAL

(1) Toxicity by the dermal route is almost always less severe than by the other routes (inhalation and oral). This is due in part to the fact that skin presents an effective barrier to absorption; *e.g.*, the presence of the stratum corneum and the thickness of epidermis and dermis combine to form a barrier superior to the lining of the gastrointestinal and respiratory tracts.

(2) The dermal LD_{50} for chlorsulfuron technical is >3400 mg/kg. In the study cited (MRID 00099460), there was one death among 5 male rabbits treated with 2000 mg/kg and, since no clinical signs were observed, this was not considered treatment-related. Additionally, there were no deaths in 10 rabbits/sex treated with 3400 mg/kg. There were no compound-related clinical signs of toxicity or gross pathology other than slight irritation at the treatment site in treated rabbits.

(3) Given the low acute dermal toxicity of chlorsulfuron and the low acute and repeated-dose dermal toxicity of other sulfonylurea herbicides, DuPont considers it extremely unlikely that a 21-day dermal study would result in a lower NOAEL/endpoint than the one selected for conducting short- and intermediate-term residential and occupational dermal risk assessments (oral endpoint of 75 mg/kg/day, based on a developmental toxicity study in rabbits).

(4) With the current oral endpoint, the dermal Margins-of-Exposure (MOEs) far exceed the target value of 300. For example, occupational exposure dermal MOEs ranged from 1100 to 75000. For residential turf application the dermal MOEs were 8800-190000. The dermal MOEs for post application exposure for residential use were 770 for toddlers and 1300 for adults.

(5) DuPont points out the fact that when the conditions of registration are satisfied (additional 3X uncertainty factor for an incomplete data base), the target MOE should be lowered to 100.

DuPont states that dermal is the primary exposure component for any of the occupational or residential risk assessments on chlorsulfuron. In order for the combined (route) risk assessments to fall below the target MOE of 300, the dermal component would have to be half the current value; *i.e.*, chlorsulfuron would have to be more than twice as toxic by the repeated-dose dermal route than with the current oral endpoint. Based on the low acute dermal toxicity of chlorsulfuron, the generally lower toxicity from dermal exposure *vs* oral exposure, and the adequate MOEs for dermal exposure to chlorsulfuron using an oral endpoint, DuPont concludes that the requirement of a 21-day dermal study is not warranted.

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