UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

Office of Prevention, Pesticides
and
Toxic Substances

February 7, 2001

MEMORANDUM

SUBJECT: MOLINATE - Comparison of HED Revised Human Health Risk Assessment for Molinate dated January 9, 2001 and California EPA Department of Pesticide Regulation (DPR) Health Assessment, The Evaluation of Molinate as a Toxic Air Contaminant, dated March 3, 2000

DP Barcode: D272593
PC Code: 041402
Submission: S592417

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Action Requested: Compare California EPA and HED's findings on molinate.

Recommendations: A comparison of dose and endpoints for the California EPA Department of Pesticide Regulation (DPR) Health Assessment and the HED Revised Human Health Risk Assessment for Molinate dated January 9, 2001 is not possible because of the objectives of the respective risk assessments. DPR only assessed risks from exposure to molinate in ambient air, whereas HED assessed risks from aggregate exposure to molinate in food and water and occupational risks. However, a comparison of respective positions on the following four toxicology issues, which are pivotal to implementation of Proposition 65 in California, has been conducted and is presented in this review: delayed neurotoxicity (hen), reproductive toxicity, carcinogenicity and developmental neurotoxicity.

Comparison of HED and DPR Risk Assessments

The DPR Health Assessment considered risks from exposure to molinate in ambient air alone, whereas the HED risk assessment evaluated dietary and occupational exposure. The risks of ambient air exposure to molinate in the vicinities near application areas were not assessed by HED, as there is no current guidance on performing these assessments. Therefore, a comparison of dose and endpoints used for the respective risk assessments is not possible.

The major issues of interest expressed in meetings with stakeholders after issuance of the initial HED risk assessment (June 15, 2000) has been the results and interpretation of the toxicology studies. Therefore, this review will focus on four toxicology issues and compare how HED and DPR interpreted the results of various studies.

1) Delayed Neurotoxicity (Hen)

The January 9, 2001 HED revised risk assessment concluded that molinate is positive for delayed neurotoxicity in the hen. This was also HED's position in the June 15, 2000 risk assessment. After meetings and conference calls with several stakeholders, including, among others, the registrant, California Rice Commission and USDA, the hen study (MRIDs 00133562 and 4313660) was forwarded to Dr. Karl Jensen at EPA's National Health and Environmental Effects Research Laboratory for his opinion on the findings. He concluded that the data indicate that molinate produces delayed neurotoxicity in the hen. A copy of his January 12, 2001 memorandum is attached to this review.

The DPR Health Assessment concluded that molinate inhibits neurotoxic esterase and such inhibitory activity is usually associated with classical Organophosphate-Induced Delayed Neuropathy (OPIDN). However, the effects due to molinate were not delayed and were not the same type of histopathology changes seen with organophosphate poisoning.

2) Reproductive Toxicity

The January 9, 2001 HED revised risk assessment stated that evidence of reproductive toxicity was found in studies in rats, mice and dogs; however, the male rat appeared to be the most sensitive species and sex. It is the registrant's position that reproductive toxicity is limited to male rodents. HED concluded that studies conducted to demonstrate a mechanism for the reproductive toxicity in male rats were not adequate.

The DPR Health Assessment concluded that reproduction effects were observed in male rats, mice and rabbits treated directly with molinate, in female rats, mice and rabbits mated with treated males and in female rats and mice treated directly. The assessment states that mechanistic studies do not fully support the argument for rodent specificity, which is in agreement with HED's conclusion.

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Due to a difference in the opinion of the toxicology reviewers, HED and DPR did differ on certain findings and determination of NOAELs/LOAELs[1] of some of the numerous reproduction studies included in the molinate data base. A detailed comparison for individual studies will not be included in this review. However, HED and DPR are in agreement in the overall conclusion that molinate alters reproduction parameters in males and females of multiple species.

3) Carcinogenicity

Molinate was recently reconsidered by the HED Cancer Assessment Review Committee (CARC) based on new data and a re-analysis of the rat kidney tumor data. The CARC classified the data from the carcinogenicity studies as "suggestive evidence of carcinogenicity but not sufficient to assess human carcinogenic potential" based on the limited evidence of kidney tumors in rats. The CARC further recommended that a dose-response assessment is not indicated for molinate (CARC report dated December 14, 2000).

The DPR Health Assessment disputes the linear approach previously used by HED. In doing the cancer risk assessment for exposure to molinate in ambient air, both linear and non-linear (Margin of Exposure) approaches were used by DPR.

In summary, HED did not conduct a dose-response assessment for the carcinogenic potential for molinate, whereas DPR has performed both linear and non-linear assessments.

4) Developmental Neurotoxicity

The January 9, 2001 HED revised risk assessment concluded that developmental/developmental neurotoxicity was observed at dose levels below the maternal NOAEL. In the rat developmental study (MRID 41473401), the maternal NOAEL was 35 mg/kg/day based on decreased body weight, body weight gain and food consumption, increased salivation and dehydration and RBC cholinesterase inhibition at 140 mg/kg/day (LOAEL). The developmental NOAEL was 2.2 mg/kg/day based on increased runting at 35 mg/kg/day (LOAEL). In the developmental neurotoxicity study in rats (MRID 44079201), the maternal NOAEL was 75 ppm (6.9 mg/kg/day) based on decreased body weight, body weight gain and food consumption at 300 ppm (26.1 mg/kg/day) (LOAEL). There was no developmental neurotoxicity NOAEL based on increased startle amplitude in the auditory startle test in females on day 23 at 20 ppm (1.8 mg/kg/day), the lowest dose tested. The FQPA Safety Factor Committee concluded that the FQPA Safety Factor should be retained at 10X for molinate based, in part, on the findings of the these two studies (December 17, 1998 Committee report).

DPR also concluded that molinate can cause developmental neurotoxicity; however, there were differences with HED in the interpretation of the findings for some studies. In the developmental

[1] The DPR Health Assessment uses the term NOEL instead of NOAEL.

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rat study, DPR concluded that the maternal NOEL was 35 mg/kg/day based on decreased food consumption and body weight and increased clinical signs at 140 mg/kg/day. The developmental NOEL was 35 mg/kg/day based on increased fetal resorption, decreased litter size and evidence of intrauterine growth retardation at 140 mg/kg/day. For the developmental neurotoxicity study, DPR concluded that the maternal NOEL was 7.5 mg/kg/day based on decreased food consumption and body weight during gestation and lactation at 30 mg/kg/day. The developmental NOEL was 7.5 mg/kg/day based on increased pup mortality and decreased body and brain weight in male and female offspring at 30 mg/kg/day. The developmental neurotoxicity NOEL was 2 mg/kg/day based on reduced thickness of the molecular layer of the prepyramidal fissure of the cerebellum (day 12) at 7.5 mg/kg/day. Therefore, DPR also determined that offspring developmental neurotoxicity effects were observed at doses below the maternally toxic dose

HED and DPR agreed on the doses and endpoints for the rabbit developmental toxicity study, which did not show any evidence of increased fetal sensitivity.

In summary, while both agencies agree that molinate produces developmental neurotoxicity, HED concluded that there is no NOAEL for the developmental neurotoxicity study, whereas DPR established a NOEL of 2 mg/kg/day.

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