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California Environmental Protection Agency

State of California
Pete Wilson, Governor

OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

MEMORANDUM

To: Larry Nelson, Ph.D., Chief
Medical Toxicology Branch
Department of Pesticide Regulation
1020 N Street, Room 234
Sacramento, CA 95814

From: Anna M. Fan, Ph.D., Chief
Pesticide and Environmental Toxicology Section

Date: March 7, 1994

Subject: Molinate Use for 1994

Staff of the Pesticide and Environmental Toxicology Section have reviewed the document on molinate. The primary comments are listed below. The detailed comments are provided in the attachment.

1. The ENEL of 0.03 mg/kg-d should be used for chronic exposures.

2. Use of the ENEL shown above would lower the calculated MOS for occupational exposures, resulting in two work tasks with an MOS of less than 100 (77 and 83), considered to be inadequate for health protection.

3. It is difficult to follow the exposure calculations. In particular, there are inconsistencies regarding the daily bag limits for molinate loading as presented in the document.

Thank you for providing us the document for review. If you have any questions, please call me at 510/540-3063 or Dr. Joy Wisniewski at 8/467-7324.

Cc: Joy Wisniewski, Ph.D.
Robert Howd, Ph.D.

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MEMORANDUM

TO: Anna M. Fan, Ph.D., Chief
Pesticide and Environmental Toxicology Section

FROM: Joy A. Wisniewski, Ph.D. RAH for JAW
Associate Toxicologist

DATE: March 7, 1994

SUBJECT: Review of Molinate Risk Assessment for the 1994 Use Season

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I have reviewed the draft molinate risk assessment for the 1994 use season that was prepared by the Department of Pesticide Regulation (February 25, 1994 version). This document provides an estimate of the health risk from occupational exposure to molinate only; it does not discuss the risks to the general population. Dr. Roger Cochran, Medical Toxicology, currently is preparing the final risk characterization document for molinate, which will include occupational and non-occupational risks, and will cover all potential exposure routes. However, it will not be completed prior to the 1994 use season.

A summary of the 1994 risk assessment and my comments are provided below.

Toxicological Assessment

Acute/short-term, subchronic, and chronic animal studies were evaluated to determine a no-observed-effect level (NOEL) for acute, seasonal, and annual exposure scenarios, respectively. For acute/short-term exposures, a NOEL of 11.5 mg/kg-day was selected. This was based on reduced fertility in male rats exposed for 5 days to molinate (other dose levels not stated). Other effects described in additional studies included developmental effects (increased resorptions and intrauterine growth retardation) and cholinergic signs.

For the seasonal exposure scenario (i.e., molinate use only during a six-week period in May and June each year), a NOEL was selected from a 5-week gavage study in male rats. The NOEL, 0.48 mg/kg-day, was based on sperm abnormalities (by scanning electron microscopy). A similar NOEL of 0.44 mg/kg-day was obtained in a two-generation reproductive study using rats, where

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histopathological changes in the ovaries were reported in female rats. However, these changes did not correlate with female infertility observed in the same study, so the toxicological significance of these results was questioned. Therefore, the NOEL based on sperm abnormalities was considered appropriate to characterize worker risks from seasonal exposure to molinate.

The seasonal NOEL changed from that which was used for the 1993 use season, i.e. 0.26 mg/kg-day. That NOEL also was based on sperm abnormalities observed in a 5-week gavage study, but the lowest-observed-effect level (LOEL) was 4.6 mg/kg-day. A subsequent study with more dose levels was done to better define the NOEL, and it was from this study that the NOEL of 0.48 mg/kg-day was determined.

Chronic molinate exposure was not considered in past use seasons as a relevant exposure scenario, because molinate is only used for six weeks out of the year. However, the re-evaluation of several chronic animal studies by Medical Toxicology staff indicated that one of the toxicological endpoints, peripheral neuropathies, may be irreversible. The lowest NOEL from a chronic study was 1.0 mg/kg-day, based on intermittent clinical signs, i.e, abnormal postural reactions, in dogs exposed to 10, 50, and 100 mg/kg-day molinate for one year. (Note that the dogs in the 100 mg/kg-day dose group were only treated for 106 days, due to severe functional deficits, and were observed until the end of the study. This group of dogs did not show any evidence of recovery after treatment with molinate ceased.) A two-year chronic rat study showed skeletal muscle atrophy, peripheral nerve degeneration, and distal spinal cord changes at all dose levels (0.3, 1.9, 17, and 29 mg/kg-day). Because there was no NOEL, an estimated no-effect level (ENEL) was calculated by applying a 10-fold uncertainty factor to the LOEL of 0.3 mg/kg-day, i.e., the ENEL = 0.03 mg/kg-day. Since this value was derived from a lifetime study, it was not considered by DPR to be relevant to the seasonal intermittent exposures that are experienced by humans. The one-year dog study was considered relevant (chronic, but not a lifetime exposure); therefore, the NOEL from the dog study was used by DPR to characterize annual occupational exposures to molinate.

We agree with Medical Toxicology on the choice of NOELs for acute and seasonal exposure. However, we recommend that the ENEL of 0.03 mg/kg-day from the two-year rat study be used for chronic exposure, rather than the NOEL of 1.0 mg/kg-day from the one-year dog study. Our rationale for this recommendation is as follows:

1) The NOEL selected for chronic exposure (1 mg/kg-day) is greater than the NOEL for subchronic exposure (0.48 mg/kg-day). Molinate use conditions based on this value may protect a chronically-exposed individual from neurotoxicity, but will not protect that individual

from reproductive toxicity. Additionally, choosing a NOEL for chronic exposure that is greater than that for subchronic exposure does not follow standard risk assessment guidelines.

2) DPR states that the one-year dog study is more relevant than the lifetime (two-year) rat study to the seasonal exposures experienced by humans. We do not agree. Because of the nature of the toxicological endpoint for chronic exposure, i.e., peripheral nerve degeneration and demyelination, especially of the long nerves, as well as the apparent irreversibility of this effect, and therefore, potential additive response from repeated seasonal exposures, we consider the lifetime NOEL (ENEL) relevant and more health protective.

Exposure Assessment and Margins of Safety

Occupational exposures for 1994 were estimated from new data submitted by the registrant for the 1993 use season. However, residential exposures were not provided in this interim risk characterization, as mentioned previously.

Occupational exposures were provided for the following work tasks: drivers, with and without carbon suits; direct loaders with either Tyvek or carbon suits; and direct and transfer loaders with either Tyvek or carbon suits. We had some difficulty following the exposure calculations, especially since there were inconsistencies between Worker Health and Safety and Medical Toxicology regarding the daily bag limit or weight limit for molinate loading. For example, the limit for direct and transfer loaders provided by Medical Toxicology is 5000 lb (Table 1), but Worker Health and Safety assumes a 10,000 lb limit (12/22/93 memo from T. Formoli to R. Cochran). Additionally, it is unclear whether the textual description of the data presented in Table 1. (p. 3) as the geometric mean and range of the absorbed daily dosage refers to the Medical Toxicology data, or to the data presented in Table 1 of Formoli (1993). It appears that the absorbed daily dosages presented by Medical Toxicology are actually arithmetic means and standard deviations, rather than geometric means. Otherwise, the calculations and final absorbed daily dosages for the three exposure scenarios appear appropriate and acceptable.

The margins of safety (MOS) for acute and seasonal exposures are acceptable. Those for chronic exposures, recalculated using the ENEL of 0.03 mg/kg-day, would change to:

Work Task	MOS
Driver (no suit)	500
Driver (carbon suit)	750

Direct loader (Tyvek)	77
Direct loader (Carbon)	120
Direct + trans. (Tyvek)	111
Direct + trans. (Carbon)	83

Typically, MOS greater than or equal to 100 are considered adequate and health-protective. DPR may want to consider additional poundage limits for the two tasks listed above that have MOS less than 100.

As mentioned previously, this risk characterization document did not provide an estimate of potential risk of molinate exposure for the general population. While monitoring data from past years have shown that residential exposures are not a health concern, DPR should provide some statement to that effect if it is still accurate. The recent data on possible irreversible neurotoxic effects in animals from chronic exposure to low levels of molinate raise concern that residents near rice fields may be at risk for similar neurotoxic effects. This issue needs to be addressed for the 1994 molinate use season.

If you have any questions pertaining to this review, please feel free to contact me at ATSS 8/467-7324.

cc: Robert Howd, Ph.D.
Michael J. DiBartolomeis, Ph.D.