4-20-88

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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: AZODRIN (Monocrotophos) - Addendum to Prior Review of the Rabbit Teratology Study Submitted under Accession No. 401023-01.
EPA Registration No. 352-459

TB Project No.: 8-0063
Caswell No.: 377

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On May 18, 1987, the review and evaluation (TB Document No. 005885) of the following study (submitted in response to reregistration data requirements) was sent to the Registration Division (Willian Miller/Gary Otakie):

Developmental Toxicity Study of AZODRIN® Insecticide (Technical) in New Zealand White (NZW) Rabbits, performed by Argus Research Laboratories, Horsham, PA, Argus Protocol No. 619-005/Haskell Lab. Report No. 014-87, dated January 12, 1987.

We concluded that the study was CORE-MINIMUM DATA, with the following parameters:

Maternal NOEL = 1 mg/kg/day
Maternal LEL = 3 mg/kg/day (fecal disturbances)
Developmental NOEL = 1 mg/kg/day

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Developmental LEL = 3 mg/kg/day (agenesis of intermediate lobe of the lung)

A/D Ratio = 1.00
(Doses tested = 0, 0.1, 1.0, 3.0, and 6.0 mg/kg/day)

The text of our review also discussed the reported occurrence in does treated at the highest dose tested (HDT), 6 mg/kg/day, of the statistically significant increase in maternal deaths, decreased weight gain, clinical signs of organophosphate toxicity and gross pathological lesions (multiple gastric as well as duodenal ulcerations, pulmonary edema, and enlarged gallbladders). As is also clearly evident in the study report, there was a dose-dependent trend for these effects which included the next lower dose level, 3 mg/kg/day, as well as the HDT (although the effects were not statistically significant at the lower dose). In addition, the investigators recorded three 3 mg/kg group rabbits with alopecia and/or soft/dried feces that delivered prematurely (Days 27 to 29 of the study). Such spontaneous delivery was suggested by the authors as a compound-related effect, despite the zero incidence at other dose levels (including the HDT), as well as in controls. (It was further suggested that the increased mortality at the HDT, namely, 13 of 20 animals, may have diminished the likelihood of observing prematurity.) Finally, only gastric ulcerations were found on necropsy in the three mid-dose does that delivered prematurely, in two of which enlarged gallbladders were also found.

Therefore, the "one-liner" description of maternal effects at 3 mg/kg/day (the LEL) should be enlarged to include the effects considered to be compound-related (additions underlined):

Maternal NOEL = 1 mg/kg/day
Maternal LEL = 3 mg/kg/day (death of one dam, gastrointestinal ulceration, premature delivery, fecal disturbance)

Developmental NOEL = 1 mg/kg/day
Developmental LEL = 3 mg/kg/day (agenesis of intermediate lobe of lung)

A/D Ratio = 1.00
(Doses tested = 0, 0.1, 1.0, 3.0, and 6.0 mg/kg/day)