

MEMORANDUM

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DATE: December 19, 2003

SUBJECT: COMMENTS ON THE DEPARTMENT OF PESTICIDE
REGULATION'S DRAFT RISK CHARACTERIZATION DOCUMENT
FOR THE ACTIVE INGREDIENT HYDRAMETHYLNON

We have completed our review of the draft risk characterization document (RCD) for tetrahydro-5,5-dimethyl-2 (1H)-pyrimidinone {3[4-(trifluoromethyl) phenyl]-1-[2-(4-trifluoromethyl) phenyl] ethenyl]-2-propenylidene} hydrazone (hydramethylnon) prepared by the Department of Pesticide Regulation (DPR).

Hydramethylnon {tetrahydro-5,5-dimethyl-2 (1H)-pyrimidinone {3[4-(trifluoromethyl) phenyl]-1-[2-(4-trifluoromethyl) phenyl] ethenyl]-2-propenylidene} is an insecticide used to control ants (including imported fire ants and leafcutter ants), cockroaches and termites. Hydramethylnon is used on a single food crop (pineapple), on feed (rangeland grasses, and hay) and also has non-food uses (lawns, turfs, golf courses, non-bearing nursery stocks, right-of-ways, houses and other structures). The use of hydramethylnon on pasture and rangeland grass is not permitted in California. Hydramethylnon was first registered with the U.S. EPA in 1980. It belongs to a chemical class of chemicals known as the trifluoromethyl amidinohydrazones. It is listed as a reproductive and developmental toxicant under Proposition 65.

Overall, we support the procedures and approaches used for characterizing the health risk of hydramethylnon in the draft RCD for this chemical. We especially acknowledge efforts made to substantiate the choices of critical studies, discussions of issues that might be raised by reviewers, identification of numerous uncertainties pertinent to risk estimates, and comparison of risk estimates with those estimated by the U.S. EPA. While the current version of the draft RCD is quite thorough, it would benefit from clarifying certain issues and expanding the information provided.

A summary of our comments on the draft RCD for methyl hydramethylnon is found below. For more details please refer to the attachment.

1. While OEHHA supports DPR's choices of critical studies, toxicological endpoints and NOAELS used in the RCD for hydramethylnon, we note that seasonal (subchronic oral) exposures are not evaluated in the document. No support for this decision is provided in the RCD. We suggest that DPR either evaluate this exposure scenario or provide appropriate justification for not evaluating subchronic exposures.
2. OEHHA agrees that inhalation exposure to hydramethylnon is likely negligible, however, only limited discussion is provided in the RCD supporting this assumption. We note that the U.S. EPA performed this assessment, finding that exposure from the inhalation pathway is indeed negligible. We suggest either evaluating this route in the RCD or substantiating that the exposures evaluated by the U.S. EPA are similar enough to those expected in California and cite the federal assessment as additional support for this assumption.
3. We support the overall evaluation for carcinogenicity. The report includes several important analyses. The report would further benefit by discussing the value of applying an additional uncertainty factor for possible carcinogenicity for chronic exposures.
4. Even though a developmental toxicity endpoint was not used for calculating MOEs in the RCD, we suggest that DPR provide further justification for the selection of 10 mg/kg/day as the NOAEL for developmental toxicity instead of the value of 5 mg/kg/day as determined by the U.S. EPA.
5. No potentially sensitive subpopulations are discussed in the RCD other than children and infants. OEHHA recommends a brief discussion of other potentially sensitive subpopulations (elderly, medical conditions) be added to the document.
6. It is unclear if hydramethylnon is applied to pineapples in California. We suggest clarifying this in the RCD.
7. OEHHA recommends including in the RCD specific information regarding existing (or lack of) current exposure benchmarks such as the reference dose, maximum contaminant level, threshold limit value, and permissible exposure limits etc.

Thank you for providing the document for our review. If you have any questions about our comments, please contact Dr. Jolanta Bankowska at (510) 622-3162 or Mr. Robert Schlag at (916) 323-2624.

Attachment

ATTACHMENT

COMMENTS ON THE DRAFT RISK CHARACTERIZATION DOCUMENT FOR HYDRAMETHYLNON

BACKGROUND INFORMATION

Hydramethylnon {tetrahydro-5,5-dimethyl-2 (1H)-pyrimidinone {3[4-(trifluoromethyl) phenyl]-1-[2-(4-trifluoromethyl) phenyl] ethenyl]-2-propenylidene} is an insecticide used to control ants (including imported fire ants and leafcutter ants), cockroaches and termites. Hydramethylnon is used on a single food crop (pineapple), on feed (rangeland grasses, and hay) and also has non-food uses (lawns, turfs, golf courses, non-bearing nursery stocks, right-of-ways, houses and other structures). The use of hydramethylnon on pasture and rangeland grass is not permitted in California. Hydramethylnon was first registered with the U.S. EPA in 1980. It belongs to a chemical class of chemicals known as the trifluoromethyl amidinohydrazones. It is listed as a reproductive and developmental toxicant under Proposition 65.

Our specific comments are provided below:

COMMENTS

Selection of critical studies and endpoints for risk assessment in RCD:

Acute Toxicity:

An estimated acute NOAEL of 3 mg/kg/day (0.3 mg/kg/day, absorbed dose) was selected to calculate margin of exposures (MOE) for acute dietary exposures to hydramethylnon. This NOEL was estimated from a LOAEL of 30 mg/kg/day that was based on decreased body weight, clinical signs (nasal and perianal area bloody discharges), and reduced fertility in rats given hydramethylnon for five days (Harnois, 1979). The risk from acute dermal exposure was calculated using a NOAEL of 50 mg/kg/day (0.1 mg/kg/day, absorbed dose) based on decreased food consumption in a rabbit 21-day dermal toxicity study (Thompson, 1982) at the next higher dose of 250 mg/kg/day. Health risks from inhalation exposure to hydramethylnon were not assessed because it is unlikely that the chemical will be found in the air (low vapor pressure and low Henry's Law constant).

Subchronic Toxicity:

A NOAEL of 50 mg/kg/day (1.8 mg/kg/day, absorbed dose) was used to calculate the MOEs for subchronic (seasonal) exposure. This NOAEL was derived from a dermal study in rabbits, which showed decreased food consumption at the next higher dose of 250 mg/kg/day (Thompson, 1982). Subchronic oral exposures were not evaluated in the RCD.

Chronic Toxicity:

Chronic dietary exposure was assessed based on an estimated NOAEL of 1 mg/kg/day (0.1 mg/kg/day, absorbed dose) determined in a 26-week gavage dog study (Marshall, 1980). Toxicological effects observed in this study were clinical signs (soft stools, mucoid stools, diarrhea) and weight loss seen at the next higher dose (LOAEL) of 3 mg/kg/day (0.3 mg/kg/day absorbed dose).

While OEHHA supports DPR's choices of critical studies, toxicological endpoints and NOAELS used in the RCD for hydramethylnon, we note that seasonal (subchronic oral) exposures are not evaluated in the document. No support for this decision is provided in the document. We suggest that DPR either evaluate this exposure scenario or provide appropriate justification for not evaluating subchronic exposures.

Absorption of hydramethylnon by different routes of exposure

Exposure estimates and MOEs were calculated in the RCD by using ten percent oral, and five percent dermal absorption. These absorption factors were determined from the results of the study by Zdybak and Robison (1992) for oral absorption and for dermal absorption from two studies (Frantz and Beskitt, 1993; Sharp 1993).

Exposure to hydramethylnon via the inhalation route was considered negligible and therefore not assessed in the RCD. This decision is supported by physico-chemical properties of the active ingredient (low volatility and low Henry's Law constant) and formulations used (granular/flake, pellet/tablet/cake/briquette, gel/paste/cream, impregnated material, or dry material).

OEHHA agrees that inhalation exposure to hydramethylnon is likely negligible, however, only limited discussion is provided in the RCD supporting this assumption. We note that the U.S. EPA performed this assessment, finding that exposure from the inhalation pathway is indeed negligible. We suggest either evaluating this route in the RCD or substantiating that the exposures evaluated by the U.S. EPA are similar enough to those expected in California and cite the federal assessment as additional support for this assumption.

Reproductive and developmental toxicity

Hydramethylnon causes reproductive toxicity in rats. Available multiple-generation toxicity studies (Biodynamics, Inc., 1982; Schroeder, 1995) showed non-reversible reduced fertility in rats, the target organ was the testis. An adult NOAEL of 1.66 mg/kg/day (0.017 mg/kg/day absorbed dose) based on adverse effects in the testis, consisting of degeneration of the germinal epithelium and aspermia, and epididymis-increased cellular debris was identified (Schroeder, 1995) and was used by the U.S. EPA to assess chronic dietary exposure and acute, subchronic and chronic exposures by the dermal and inhalation routes.

Developmental toxicity studies with hydramethylnon in rats and rabbits showed reduced body weight gain, yellow body fats, and clinical signs such as soft stool and anogenital stains (Bio/dynamics Inc., 1979; IRDC 1982c). In the first study a developmental NOAEL 10 mg/kg/day was identified based on decreased fetal weight and ossification variations (attributed to the body weight loss in the dams) at the next higher dose of 30 mg/kg/day. The maternal NOAEL in this study was lower, 3 mg/kg/day, and was based on decreased body weight gain at the next higher dose of 10 mg/kg/day. In the second study (IRDC 1982c) a NOAEL for maternal toxicity of 5 mg/kg/day based on decreased body weight gain and clinical signs such as reduced stool amounts or soft stools, yellow body fat, and matting and/or discharge in anogenital region at the next higher dose of 10 mg/kg/day was identified. A NOAEL of 5 mg/kg/day was also identified in this study for developmental toxicity based on an increase in spontaneous abortions at the next higher dose of 10 mg/kg/day. The NOAEL of 10 mg/kg/day for developmental toxicity based on decreased fetal weight was identified by DPR from the Bio/dynamics Inc., 1979 study as the NOAEL for developmental toxicity. The U.S. EPA selected 5 mg/kg/day from the IRDC, 1982c study as the NOAEL for developmental toxicity.

Even though a developmental toxicity endpoint was not used for calculating MOEs in the RCD, we suggest that DPR provide further justification for the selection of 10 mg/kg/day as the NOAEL for developmental toxicity instead of the value of 5 mg/kg/day as determined by the U.S. EPA.

Groups sensitive to hydramethylnon exposures

Available toxicological data do not provide evidence for increased pre- and post-natal sensitivity when NOAELs for developmental or reproductive toxicity are compared with those for maternal toxicity. Indeed, in both rat and rabbit developmental toxicity studies, maternal NOAELs were equal to or even lower than fetal NOAELs. Significant effects in the fetuses included reduced fetal body weights (rats and rabbits) and ossification variations (rats only). Similarly, no effects were observed in pups at levels lower than those resulting in maternal and/or reproductive effects. In conclusion no additional safety factor is needed to protect infants and children as is required by the Food and Quality Protection Act (FQPA).

No other sensitive group of the human population is mentioned or discussed in the document. OEHHA recommends including a discussion of other potentially sensitive subpopulations (elderly, medical conditions) in the RCD.

Potential oncogenic effects

Hydramethylnon is classified by the U.S. EPA as a possible human carcinogen (group C carcinogen). Available long-term toxicity studies showed treatment-related tumors in the mouse (IRDC, 1982b) but not in the rat (IRDC, 1982a). Tumors (adenomas and carcinomas) were observed in lungs of female mice. Statistical analysis showed significant increases in lung adenomas and combined adenomas/carcinomas at all doses

studied versus the controls. We concur with DPR's use of time-dependant statistical analysis of the incidence data for pair-wise analysis and trend analyses. It was especially important for these data due to the differential survival in the treatment groups. It would also be useful to provide time-dependent analysis with including the highest dose group.

There were also lung tumors found in male mice but they were considered not to be toxicologically significant since the incidences were increased only at maximally tolerated dose (MTD). Uterine polyps were also observed in female rats at the MTD and were also considered not significant since the incidences were increased at maximally tolerated doses. However, as indicated in Table 15, there was a statistically significant trend. Consequently, the effect does not appear to be related solely to exceeding the MTD.

We note that Dr. Hathaway in his December 16th 1988 testimony before the Proposition 65 Scientific Advisory Panel states: "the adrenal medullary tumors in CD rats the MTD was exceeded in that. It is an equivocal study. There was some indication at a lower dose, but not statistically significant". It also would be useful to provide the incidence rate and detailed analysis, similar to Table 26, in the report for this tumor cite. Available genotoxicity tests were all negative. The overall weight of evidence evaluation indicates suggestive evidence for oncogenicity, but does not justify performing a carcinogenic risk assessment.

We support DPR's overall weight of evidence evaluation that includes discussion of the U.S. EPA approach, genotoxicity studies and consideration of structure-activity relationships. This is consistent with the California Proposition 65 Scientific Advisory Panel's determination in 1989 to not add hydramethylnon to the list of carcinogens Scientific Advisory Panel 1988, pg. 59). Since there is "suggestive " evidence for hydramethylnon carcinogenicity the RCD would benefit by discussing the value of applying an additional uncertainty factor for possible carcinogenicity for chronic exposures.

Use of hydramethylnon in California

It is not clear in the RCD whether hydramethylnon uses in California are limited solely to non-food applications (see first paragraph on page one and second paragraph on page six) or if it is also registered for use on pineapples. We suggest this issue be clarified in the RCD.

Exposure standards

OEHHA recommends including in the RCD specific information regarding existing (or lack of) current exposure benchmarks such as the reference dose, maximum contaminant level, threshold limit value, permissible exposure limits, etc.

References

Bio/dynamics, Inc., 1979. Teratogenicity study in rats with AC 217,300. Bio/dynamics Project no. 79-2382. American Cyanamid Company. DPR Vol. 395-007#993338.

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