OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

MEMORANDUM

TO: Larry L. Nelson, Ph.D., Chief
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FROM: Anna M. Fan, Ph.D., Chief
Pesticide and Environmental Toxicology Section

DATE: November 15, 1993

SUBJECT: Hydrogen Cyanamide Risk Characterization

In response to your request for an expedited review of the draft risk characterization document on hydrogen cyanamide, staff of the Pesticide and Environmental Toxicology Section (PETS) have prepared a report providing comments as shown in the attachment. The report provides details relating to particular issues and suggestions for the next version of the document, and the major conclusions and recommendations are summarized as follows. Overall we find this document to be well-written and to cover the majority of the information needed to assess the risks of this active ingredient.

CONCLUSIONS/RECOMMENDATIONS

1. The Margin of Safety for potential short-term exposure should be based on the lowest value for a NOEL identified in acute-exposure type studies such as developmental toxicity studies. In this case it should be 2 mg/kg-day and not 5 mg/kg-day as in the DPR document.

2. The potential of hydrogen cyanamide for causing dermal sensitization should be addressed in the main part of the risk characterization document.

3. The characterization of oncogenicity should be strengthened by addressing structure-activity relationship.

4. Data presented on exposure assessment in two different seasons clearly show that recommendations of mitigation measures do not work unless a reliable enforcement system exists.

5. No recommendations are provided in the document to mitigate the magnitude of exposure to hydrogen cyanamide in field supervisors.

6. It would be useful to discuss separately hydrogen cyanamide's potential for reproductive toxicity under the "Risk Characterization" section of the document. Also, the issue of identifying a NOEL for hormonal and spermatogenic changes in humans should be addressed.

In summary, hydrogen cyanamide is a new active ingredient that is being considered for full registration. We have identified several issues for DPR for more detailed consideration as listed above. In general, we feel that overall more attention and thorough evaluation should be devoted to the new active ingredients than currently permitted, based on our experience on expedited reviews requested. In this regard, we would like to discuss the factors affecting the time available for evaluation and review, with the objective of enabling us to have adequate time to provide DPR with the most useful review comments.

We thank you for sending us the document for review. If you have any questions relating to our comments, please contact me at (510) 540-3066 or Dr. Michael DiBartolomeis at (510) 540-2665.

Attachment

cc: Jolanta Bankowska, Ph.D.
Michael J. DiBartolomeis, Ph.D.

ATTACHMENT

PETS Review of the California Department of Pesticide Regulation's Draft Document on Risk Characterization of Hydrogen Cyanamide

BACKGROUND INFORMATION

Hydrogen cyanamide is a new pesticide active ingredient being considered for a FIFRA Section 3 (full) registration as a plant regulator to promote uniform bud break in grape vines. It has been used in California under a Section 18 Emergency Exemption as a spray formulation, Dormex, for three of the last six years. It usually is applied on pruned grapevines between December 1 and January 31.

Currently, hydrogen cyanamide is under concurrent reviews in the Department of Pesticide Regulation (DPR) and the U.S. Environmental Protection Agency (U.S. EPA) for registration under Section 3 of FIFRA.

ADEQUACY OF THE DATA PACKAGE

Comments. According to the SB 950 requirements and the Summary of Toxicology Data prepared by DPR, there are no data gaps as of September 8, 1993. Information provided in Appendix B (see pg. 3) indicates that hydrogen cyanamide caused dermal sensitization in the laboratory tests and in humans. This issue of dermal sensitization is not addressed in the main part of the document.

PHARMACOKINETICS

Comments. Pharmacokinetic data on hydrogen cyanamide are presented clearly and succintly in the document.

TOXICOLOGICAL EVALUATION

Summary data on major toxicological studies are included here for reference use later in the comments.

Acute toxicity

Comments. The main document does not provide any information on skin sensitization.

Subchronic toxicity

The risk characterization document for hydrogen cyanamide summarizes short-term chronic toxicity studies by the oral route in rats and dogs. The main target organs

for hydrogen cyanamide toxicity are the liver, thyroid and testes. The lowest-observed-effect-level (LOEL) for hepatotoxicity (28 day dietary study) in rats was 4.6 mg/kg. In another 28-day study (gavage study) in rats the LOEL for thyroid toxicity was 5 mg/kg-day. The 90-day "no-observed-effect level" (NOEL) for thyroid toxicity in rats exposed to hydrogen cyanamide in the diet was 0.8 mg/kg-day. In the 90-day gavage study in dogs, the NOEL for thyroid toxicity (reduced plasma thyroxin levels) was 2 mg/kg-day. In the same study, the LOEL for testicular atrophy and oligospermia in dogs was 0.6 mg/kg-day.

Comments. It appears that in subchronic toxicity studies rats are more sensitive to the hydrogen cyanamide thyrotoxic effects than dogs. However, the most sensitive toxicological endpoint, testicular atrophy and oligospermia, were identified in the dog study. The NOEL for these effects was not established, but it would be lower than 0.6 mg/kg-day. If the value of 10 for the uncertainty factor (traditionally used to calculate a NOEL from a LOEL) is applied, then the NOEL for testicular atrophy and oligospermia would be 0.06 mg/kg-day.

Chronic toxicity/oncogenicity

Hydrogen cyanamide was not oncogenic in the rat, but was oncogenic in the mouse. It caused a significant, dose-related increase in benign granulosa-theca tumors in the ovary. In the rat chronic exposure resulted in thyroid toxicity (reduced colloid and the formation of micro-follicles, reduced triiodothyronine and tyroxine levels in the plasma) with the NOEL established at 1 mg/kg-day. In the mouse study, in addition to the oncogenic effects, hydrogen cyanamide caused nephrotoxicity (fibrosis and scarring, atrophic/basophilic tubules, and vacuolar degeneration and necrosis), chronic cystitis of the urinary bladder, and hepatotoxicity. The NOEL for mouse nephrotoxicity was 13.7 mg/kg-day, and for hepatotoxicity 29.5 mg/kg-day.

Toxic effects resulting from chronic oral exposure to hydrogen cyanamide in dog included thyroid toxicity (lower thyroxine levels), changed clinical chemistry indicating reduced metabolism, testicular effects (neutrophil infiltration of testes, oligospermia) and clinical signs (tremors and excessive salivation). The NOEL for these effects in dogs was 0.2 mg/kg-day.

Reproductive toxicity

In a two-generation reproductive toxicity study in rats acceptable under FIFRA no reproductive effects were reported. The NOEL identified in this study was 1.25 mg/kg-day for loss of body weight in adult rats and for neonatal pup survival (days 0-4). In an earlier, unacceptable study, dietary exposure to hydrogen cyanamide was reported to cause atrophic seminiferous tubules and interstitial cell proliferation in rats.

Comments. In spite of negative findings from the acceptable reproductive toxicity study in rats, a potential for adverse reproductive health effects from exposure to hydrogen cyanamide in humans should not be discounted. Reproductive effects caused by hydrogen cyanamide were shown in various other studies in rats, mice and dogs. Also, the negative reproductive toxicity study, despite its "acceptability" to the U.S. EPA and DPR, has some deficiencies such as a limited exposure time period that was reduced to 12 weeks instead of the usually required 14-20 weeks.

Developmental toxicity

In the teratogenicity study in rabbits, hydrogen cyanamide caused increased incidences of diaphragmatic hernias, resorptions, deaths, anomalies and variants, retinal folds, and decreased fetal weights. The NOEL for developmental effects was established at 2 mg/kg-day, and was based on increased retinal folds. The maternal NOEL, based on decreased body weight gain during pregnancy was 6 mg/kg-day.

In rats the maternal NOEL of 5 mg/kg-day was established on the basis of clinical signs such as hypoactivity, hunched posture, fecal and urine stains, protruding eyes, malocclusion, and chromodacryorrhea. The developmental NOEL was 15 mg/kg-day for reduced fetal weight and soft tissue malformations.

SPECIAL STUDIES

Dermal and Inhalation-Human

An interesting study (Mertshenk et al., 1993) on the effect of calcium cyanamide on human thyroid and reproductive system hormone levels in plasma was briefly summarized in the risk document (see pg. 20). No significant difference was found between plasma levels of TSH, thyroxine, triiodothyronine, thyroxine, binding globulin, FSH, LH, or testosterone in men exposed and unexposed to calcium cyanamide. The mean concentration of N-acetylcyanamide in the urine of exposed men was 0.75 mg/liter before work, and 2.14 mg/liter after an 8-hour work day.

Either DPR or the authors of the study concluded that "The indicated exposure was three orders of magnitude below that which would be expected to affect blood chemistry indicators of thyroid function. None of the laboratory animal data suggests that an effect on reproductive hormone levels would be expected , even at higher doses."

Comments. The information on this study provided in the DPR document does not substantiate the above conclusion. More information such as conditions of the human exposure (subchronic, chronic) and examples of the most relevant laboratory animal data should be provided to support the conclusion.

RISK ASSESSMENT

Hazard Identification

Acute. A developmental toxicity study in rats served as the basis for identifying a NOEL of 5 mg/kg-day for risk assessment of acute exposure to hydrogen cyanamide. This NOEL was based on clinical signs of maternal toxicity such as hunched posture, fecal and urine stains, protruding eyes, malocclusion, and chromodacryorrhea.

Comments. There is another developmental toxicity study available for risk assessment for potential acute exposure. In this study performed in rabbits a NOEL for developmental toxicity (retinal folds) was identified at 2 mg/kg-day. DPR should substantiate a choice of the higher (less health protective) NOEL value (5 mg/kg-day versus 2 mg/kg-day) for risk assessment purposes.

Seasonal. DPR had the challenging task of identifying the appropriate NOEL value for calculating a potential health risk from seasonal exposure to hydrogen cyanamide. The criteria used for the identification included: the most sensitive toxicological endpoint found in subchronic toxicity studies, the acceptability of the studies according to FIFRA guidelines or from a scientific viewpoint, and the applicability of the duration of the laboratory study to the observed duration of human exposure.

Comments. In general, we agree with the reasoning used by DPR to derive the value of the NOEL for calculating margin of safety from potential adverse effects from seasonal exposure to hydrogen cyanamide. The type of laboratory studies most comparable in duration to worker's seasonal exposure is subchronic toxicity studies. The most sensitive toxicological endpoints identified in subchronic toxicity studies were testicular atrophy and oligospermia in the dog (90 day gavage study). There was no NOEL for these effects established in this study. The LOEL was 0.6 mg/kg-day. Because a NOEL was not established, the estimated no effect level (ENEL) would be 0.06 mg/kg-day (using the tradional 10-fold uncertainty factor). However, a 90-day ENEL of 0.06 mg/kg-day would be less than the observed NOEL of 0.2 mg/kg-day reported in dogs after a one-year exposure (Osheroff, 1989). Consequently, the actual NOEL at 90 days is likely to be below 0.6 mg/kg-day, but above the one-year NOEL of 0.2 mg/kg-day identified in the document.

The duration of animal exposure in the rat reproduction study was also 90 days (Morseth, 1990). In this study an ENEL of 0.42 mg/kg-day was derived for neonatal survival . This ENEL and the expected 90-day NOEL for testicular atrophy in dogs (between 0.6 and 0.2 mg/kg-day) fall in the same range. DPR used the ENEL of 0.42 mg/kg-day for neonatal survival in the rat to calculate the margins of safety for seasonal exposure to hydrogen cyanamide.

While this level seems to be currently justified by the available data, we are concerned over the reproductive toxicity of hydrogen cyanamide. Testicular atrophy is very likely to be an irreversible effect preceded by changes in spermatogenesis and reproductive hormone level. There is currently no NOEL or LOEL established for the latter effects, which may occur not only earlier but also at the lower exposure level in dogs. An effort should be made to establish an NOEL level for irreversible reproductive effects caused by exposure to hydrogen cyanamide. A discussion addressing our concerns would be appropriate for the risk characterization document.

Chronic. The lowest NOEL of 0.2 mg/kg-day was identified in a one-year chronic study in dogs for thyroid toxicity, testicular effects, clinical signs, and hematological changes.

Lifetime. Currently available data suggests that hydrogen cyanamide is weakly oncogenic. It did not produce any tumors in rats. However, it did cause a dose-related increase in ovarian granulosa-theca tumors in mice. Such tumors in humans appear late in life, and slowly progress toward malignancy. They generally remain focal in the ovary.

EXPOSURE ASSESSMENT

In this risk characterization only occupational exposures were considered. Exposure through the dietary route is not expected mainly because hydrogen cyanamide is applied to dormant, trimmed grapevines, and grape residue studies showed no residues of hydrogen cyanamide. Worker exposure estimates were based on the worker exposure monitoring study by Formoli et al., 1993. The absorbed dosage of hydrogen cyanamide was estimated from urinary concentration of N-acetylcyanamide, a metabolite. It was assumed that the N-acetylcyanamide in the collected urine represented 40% of the absorbed dosage.

Estimates of the mean absorbed dosages for agricultural workers from potential daily, seasonal, annual, and lifetime exposures to hydrogen cyanamide are summarized in table 9 on page 25 of the risk document. The table contains estimates for mixer/loader, applicator, and supervisor for two seasons--1988-1989 and 1992-1993. The values for the 1992-1993 season are much higher than the equivalent values for 1988-1989. The reasons given for these differences were: 1) inclusion of corrections for losses from field samples, and 2) a reduced level of compliance with the requirement of a closed system (Formoli et al., 1993). The highest exposure estimates were obtained for supervisors who, unlike mixer/loaders and applicators, did not wear protective clothing.

Comments. Appendix B on occupational exposure assessment contains a few tables with estimates equivalent to the ones described above. The relationship of the data presented in Appendix B and the data chosen for risk assessment should be addressed more clearly.

RISK CHARACTERIZATION/APPRAISAL

Comments. Margins of Safety (MOS) for mean potential daily, seasonal, and annual absorbed dosages of hydrogen cyanamide, and the maximum likelihood for additional lifetime risk of cancer for agricultural workers, are summarized in table 10 (pg. 26). Margins of safety for the seasonal absorbed daily dosages do not appear to be adequate for applicators (84) and field supervisors (53) during 1992-1993 season. These groups showed higher exposure values during this season in comparison with 1988-1989 season (see also "Exposure Assessment"). Also, the high exposure values (and consequently lower MOS) determined for supervisors are very likely directly related to their not wearing protective clothing.

In conclusion DPR states in its document that "...in the 1992-1993 season, closed system and other required protective measure were not always used. In those circumstances, the MOSs for potential seasonal exposure of supervisors and applicators were not greater than 100. If the mitigation measures described on the current label are followed, the margins of safety are adequate."

CONCLUSIONS/RECOMMENDATIONS

1. MOS for potential short-term exposure should be based on the lowest value for a NOEL identified in acute-exposure type studies such as developmental toxicity studies. In this case it should be 2 mg/kg-day and not 5 mg/kg-day as in the DPR document.

2. The potential of hydrogen cyanamide for causing dermal sensitization should be addressed in the main part of the risk characterization document.

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5. No recommendations are provided in the document to mitigate the magnitude of exposure to hydrogen cyanamide in field supervisors.

6. It would be useful to discuss separately hydrogen cyanamide's potential for reproductive toxicity under the "Risk Characterization" section of the document. Also, the issue of identifying a NOEL for hormonal and spermatogenic changes in humans should be addressed.

SUMMARY

Hydrogen cyanamide is a new active ingredient that is being considered for full registration. We have identified several issues for DPR for more detailed consideration as listed above under the section on conclusions/recommendations. In general, we feel that overall more attention and thorough evaluation should be devoted to the new active ingredients than currently permitted, based on our experience on expedited reviews requested. In this regard, we would like to discuss the factors affecting the time available for evaluation and review, with the objective of enabling us to have adequate time to provide DPR with the most useful review comments.

References

1. Formoli, T.A., R.K Broberg, and T. Thongsinthusak, 1993. Estimation of exposure of persons in California to pesticide products that contain hydrogen cyanamide. HS 1685, September 24, 1993. Worker Health and Safety Branch, Department of Pesticide Regulation, California Environmental Protection Agency, Sacramento, CA.

2. Mertshenk, B., W. Bornemann, C.R. Pickardt, U. Rust, J. C. Schneider, and Ch. Gloxhuber, 1993. Examination on endocrine functions in employees from a calcium cyanamide production plant. Zbl. Arbeitsmed. 43: 254-258.

3. Morseth, S.L., 1990. Two generation reproduction study in rats with aqueous hydrogen cyanamide (50% w/w). Hazelton Laboratories America Report No. 2319-126 DPR Vol. 50660-75 # 116273.

4. Osheroff, M.R, 1989. Chronic toxicity study in dogs with aqueous hydrogen cyanamide. Hazleton LaboratoriesAmerica Inc. Study No. 2319-121. DPR Vol. 500660-037 # 085351.